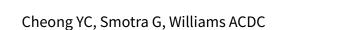


**Cochrane** Database of Systematic Reviews

# Non-surgical interventions for the management of chronic pelvic pain (Review)



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#### [Intervention Review]

# Non-surgical interventions for the management of chronic pelvic pain

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#### **ABSTRACT**

#### **Background**

Chronic pelvic pain is a common and debilitating condition; its aetiology is multifactorial, involving social, psychological and biological factors. The management of chronic pelvic pain is challenging, as despite interventions involving surgery, many women remain in pain without a firm gynaecological diagnosis.

# **Objectives**

To assess the effectiveness and safety of non-surgical interventions for women with chronic pelvic pain.

#### **Search methods**

We searched the Menstrual Disorders and Subfertility Group Specialised Register. We also searched (from inception to 5 February 2014) AMED, CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS. We handsearched sources such as citation lists, trial registers and conference proceedings.

#### **Selection criteria**

Randomised controlled trials (RCTs) on non-surgical management of chronic pelvic pain were eligible for inclusion. We included studies of women with a diagnosis of pelvic congestion syndrome or adhesions but excluded those with pain known to be caused by endometriosis, primary dysmenorrhoea (period pain), active chronic pelvic inflammatory disease or irritable bowel syndrome. We considered studies of any non-surgical intervention, including lifestyle, physical, medical and psychological treatments.

### Data collection and analysis

Study selection, quality assessment and data extraction were performed independently by two review authors. Meta-analysis was performed using the Peto odds ratio (Peto OR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes, with 95% confidence intervals (CIs). The primary outcome measure was pain relief, and secondary outcome measures were psychological outcomes, quality of life, requirement for analgesia and adverse effects. The quality of the evidence was assessed by using GRADE methods.

### **Main results**

Twenty-one RCTs were identified that involved non-surgical management of chronic pelvic pain: 13 trials were included in the review, and eight were excluded. The studies included a total of 750 women—406 women in the intervention groups and 344 in the control groups. Included studies had high attrition rates, and investigators often did not blind adequately or did not clearly describe randomisation procedures.

#### Medical treatment versus placebo



Progestogen (medroxyprogesterone acetate (MPA)) was more effective than placebo at the end of treatment in terms of the number of women achieving a greater than 50% reduction in visual analogue scale (VAS) pain score immediately after treatment (Peto OR 3.00, 95% CI 1.70 to 5.31, two studies, n = 204,  $I^2 = 22\%$ , moderate-quality evidence). Evidence of benefit was maintained up to nine months after treatment (Peto OR 2.09, 95% CI 1.18 to 3.71, two studies, n = 204,  $I^2 = 0\%$ , moderate-quality evidence). Women treated with progestogen reported more adverse effects (e.g. weight gain, bloatedness) than those given placebo (high-quality evidence). The estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm (Peto OR 0.42, 95% CI 0.11 to 1.61, one study, 39 women, low-quality evidence). Women in the lofexidine group reported more adverse effects (including drowsiness and dry mouth) than women given placebo (moderate-quality evidence).

#### Head-to-head comparisons of medical treatments

Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, 95% CI 2.08 to 3.92, one study, n = 47, moderate-quality evidence) at one year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amytriptyline (MD -1.50, 95% CI -2.06 to -0.94, n = 40, low-quality evidence). Study authors reported that no statistically significant difference was observed in the rate of adverse effects among women taking gabapentin compared with women given amytriptyline. The study comparing goserelin versus progestogen did not report on adverse effects.

#### **Psychological treatment**

Women who underwent reassurance ultrasound scans and received counselling were more likely to report improved pain than those treated with a standard 'wait and see' policy (Peto OR 6.77, 95% CI 2.83 to 16.19, n = 90, low-quality evidence). Significantly more women who had writing therapy as a disclosure reported improvement in pain than those in the non-disclosure group (Peto OR 4.47, 95% CI 1.41 to 14.13, n = 48, very low-quality evidence). No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo (quality of evidence ranged from very low to low). Studies did not report on adverse effects.

#### **Complementary therapy**

Distension of painful pelvic structures was more effective for pain when compared with counselling (MD 35.8, 95% CI 23.08 to 48.52 on a zero to 100 scale, one study, n = 48, moderate-quality evidence). No difference in pain levels was observed when magnetic therapy was compared with use of a control magnet (very low-quality evidence). Studies did not report on adverse effects.

The results of studies examining psychological and complementary therapies could not be combined to yield meaningful results.

#### **Authors' conclusions**

Evidence of moderate quality supports progestogen as an option for chronic pelvic pain, with efficacy reported during treatment. In practice, this option may be most acceptable among women unconcerned about progestogenic adverse effects (e.g. weight gain, bloatedness—the most common adverse effects). Although some evidence suggests possible benefit of goserelin when compared with progestogen, gabapentin as compared with amytriptyline, ultrasound versus 'wait and see' and writing therapy versus non-disclosure, the quality of evidence is generally low, and evidence is drawn from single studies.

Given the prevalence and healthcare costs associated with chronic pelvic pain in women, RCTs of other medical, lifestyle and psychological interventions are urgently required.

#### PLAIN LANGUAGE SUMMARY

# Non-surgical interventions for the management of chronic pelvic pain

# **Review question**

Cochrane authors considered the evidence for effectiveness and safety of non-surgical treatrments for managing chronic pelvic pain in women.

# Background

Chronic pelvic pain in women is a common problem. Specific causes are often difficult to identify, even after investigation with ultrasound and inspection of the pelvis with key hole surgery. Treatment is frequently limited to relief of symptoms obtained with a concoction of medicines. Cochrane review authors examined the evidence about non-surgical interventions for the management of chronic pelvic pain.

#### **Study characteristics**

Twenty-one randomised controlled studies were identified, of which 13 were included. Eight studies were excluded. The studies included a total of 750 women—406 women in the intervention groups and 344 women in the control groups. The interventions assessed included medical treatment and psychological, cognitive, behavioural, complementary and physical therapies. The evidence is current to February 2014.



#### **Key results**

The review concludes that evidence shows improvement of pain in women given a high dose of progestogen (50 mg medroxyprogesterone acetate) immediately post-treatment and for up to nine months after treatment. However, progestogen was associated with adverse effects such as weight gain and bloating. Women who underwent reassurance ultrasound scans and who received counselling were more likely to report improved pain than those whose treatment involved a 'wait and see' policy. Some evidence of benefit was seen with writing disclosure therapy and with distension of painful pelvic structures. No good evidence of benefit was noted with other interventions when compared with standard care or placebo.

The quality of the evidence was low or moderate for most comparisons, and in most cases evidence was derived from single small studies. Moreover, we were unable to draw meaningful conclusions on quality of life and physical and functional outcomes because of the large variation in outcome measures used by the included studies. Many interventions identified in this review involved only single studies with small sample sizes. Additional studies will be required in the future to replicate results obtained with the use of specific medical interventions.

# SUMMARY OF FINDINGS

Summary of findings for the main comparison. Medical treatment compared with placebo for the management of chronic pelvic pain

Medical treatment compared with placebo for the management of chronic pelvic pain

**Population: w**omen with chronic pelvic pain

Setting: any

Intervention: medical treatment

Comparison: placebo

Outcomes	Illustrative com	parative risks* (95% CI)	Relative effect (95% CI)	No. of partici- pants	Quality of the evidence	Comments	
	Assumed risk	Corresponding risk	(33 % Ci)	(studies)	(GRADE)		
	Placebo	Medical treatment					
Improvement in pain score at end of treatment: progesterone versus placebo	24/85	541 per 1000 (401 to 676)	Peto OR 3.00 (1.70 to 5.31)	204 (two studies)	⊕⊕⊕⊝ moderate <sup>1,2</sup>	Improvement defined as ≥ 50% reduction in VAS pain score	
Improvement in pain score (up to nine months after treatment): progesterone versus placebo	27/85	493 per 1000 (355 to 633)	Peto OR 2.09 (1.18 to 3.71)	204 (two studies)	⊕⊕⊕⊝ moderate <sup>1</sup>	Improvement defined as ≥ 50% reduction in VAS pain score	
Weight gain: progesterone versus placebo	14/40	808 per 1000 (638 to 909)	Peto OR 7.82 (3.28 to 18.65)	85 (one study)	⊕⊕⊕⊕ high		
Bloatedness: progesterone versus place- bo	14/40	633 per 1000 (425 to 801)	Peto OR 3.20 (1.37 to 7.47)	85 (one study)	⊕⊕⊕⊕ high		
Improvement in pain score: lofexidine versus placebo	eight/20	219 per 1000 (68 to 518)	Peto OR 0.42 (0.11 to 1.61)	39 (one study)	⊕⊕⊙⊝ low <sup>1,2,3</sup>	Improvement defined as ≥ 50% reduction in VAS pain score	
Drowsiness/lethargy: lofexidine versus placebo	eight/20	717 per 1000 (421 to 898)	Peto OR 3.80 (1.09 to 13.26)	39 (one study)	⊕⊕⊕⊝ moderate <sup>2</sup>		
Dry mouth: lofexidine versus placebo	three/20	603 per 1000 (301 to 842)	Peto OR 8.60 (2.44 to 30.31)	39 (one study)	⊕⊕⊕⊝ moderate <sup>2</sup>		

\*The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; OR: Odds ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>40% dropout rate in one of the two studies.

2> 10% dropout rate.

<sup>3</sup>Wide confidence intervals compatible with no effect or with higher rates of improvement in placebo group.

# Summary of findings 2. Medical treatment of chronic pelvic pain: head-to-head comparisons

#### Medical treatment of chronic pelvic pain: head-to-head comparisons

Patient or population: management of chronic pelvic pain

Settings: any

**Intervention:** medical treatment: head-to-head comparison

Outcomes	Medical treatment: head-to-head comparison	No. of participants (studies)	Quality of the evi- dence (GRADE)	Comments
Improvement in pelvic pain at one year: goserelin versus progestogen	Improvement in mean pelvic pain score in the goserelin group was three points greater than in the progestogen group (95% CI 2.08 higher to 3.92 higher)	47 (one study)	⊕⊕⊕⊝ moderate¹	Improvement in pelvic pain score measured on a scale of one to 100
Pain at 24 months: gabapentin versus amytriptyline	Mean pain score in the gabapentin group was 1.5 points lower than in the amytriptyline group (95% CI 2.06 lower to 0.94 lower)	40 (one study)	⊕⊕⊙⊝ low <sup>1,2</sup>	Pain score measured on a VAS scale of zero to 10

CI: Confidence interval.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>Participants not blinded. <sup>2</sup>> 10% attrition.

# Summary of findings 3. Psychological therapy compared with control interventions for the management of chronic pelvic pain

# Psychological therapy compared with control interventions for the management of chronic pelvic pain

**Population:** women with chronic pelvic pain

Setting: any

Intervention: psychological therapy Comparison: control intervention

Outcomes	Illustrative com (95% CI)	parative risks*	Relative effect (95% CI)	No. of partici- pants (studies)	Quality of the evidence (GRADE)	Comments	
	Assumed risk	Corresponding risk		(Staules)	(Class)		
	Control	Psychological therapy					
Improvement in pain scores—Ultrasound scan and counselling session versus 'wait and see'	113 per 1000	465 per 1000 (266 to 675)	Peto OR 6.77 (2.83 to 16.19)	90 (one study)	⊕⊕⊕⊝ low <sup>1</sup> ,2,6	Improvement defined as a change of five or more points on McGill Pain Questionnaire	
Improvement in pain scores—Somatocognitive therapy (Mensendieck) versus standard gynaecological clinical care	250 per 1000	530 per 1000 (244 to 797)	Peto OR 3.38 (0.97 to 11.80)	40 (one study)	⊕⊝⊝⊝ very low <sup>3,4,5</sup>	Improvement defined as ≥ 50% reduction in VAS pain score	
Improvement in pain scores—Integrated approach (somatic, psychological, dietary, environmental and physiotherapeutic factors) versus standard care	510 per 1000	613 per 1000 (425 to 773)	Peto OR 1.52 (0.71 to 3.27)	106 (one study)	⊕⊕⊝⊝ low2,5,6	Improvement defined as ≥ 50% reduction in VAS pain score	
Improvement in pain scores—Writing therapy (disclosure of pain) versus non-disclosure	200 per 1000	528 per 1000 (261 to 779)	Peto OR 4.47 (1.41 to 14.13)	48 (one study)	⊕⊕⊝⊝ very low <sup>2,7,8,9</sup>	Improvement considered an improvement of at least one point on a zero to five pain scale	
Improvement in pain scores—Psychotherapy versus placebo, measured at end of treatment	320 per 1000	271 per 1000 (101 to 549)	Peto OR 0.79 (0.24 to 2.59)	51 (one study)	⊕⊕⊕⊝ low <sup>10,11</sup>	Improvement defined as ≥ 50% reduction in VAS pain score	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>10% attrition.

<sup>2</sup>Sequence generation method not described.

<sup>3</sup>No attrition figures stated, but at one year, only 13 women in each group had completed the questionnaires.

<sup>4</sup>Unblinded.

<sup>5</sup>Wide confidence intervals compatible with no effect or with benefit from intervention.

<sup>6</sup>Participants not blinded.

<sup>7</sup>20% loss to follow-up.

<sup>8</sup>Allocation concealment methods not described.

<sup>9</sup>Unclear whether participants blinded.

 $^{10}$ Wide confidence intervals compatible with no effect or with increased pain from intervention.

1118% attrition.

# Summary of findings 4. Complementary therapy compared with control interventions for the management of chronic pelvic pain

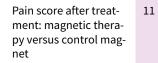
# ${\bf Complementary\ the rapy\ compared\ with\ control\ interventions\ for\ the\ management\ of\ chronic\ pelvic\ pain}$

**Population:** women with chronic pelvic pain

Settings: any

**Intervention:** complementary therapy **Comparison:** control intervention

Outcomes	Illustrative com	parative risks* (95% CI)	Relative effect (95% CI)	No. of partici-	Quality of the evidence	Comments	
	Assumed risk	Corresponding risk	(33 /6 Ci)	(studies)	(GRADE)		
	Control	Complementary therapy					
Reduction in pain score: distension of painful pelvic struc- tures versus coun- selling	23	Mean reduction in pain score in the intervention group was 35.8 higher (23.08 higher to 48.52 higher)	-	48 (one study)	⊕⊕⊕⊝ moderate <sup>1</sup>	Reduction in pain score, measured on a self as- sessed one to 100 VAS scale	



Mean pelvic pain score in the intervention group was 0.5 lower (1.92 lower to 0.92 higher)

19 ⊕⊝ (one study) ver

⊕⊝⊝⊝ very low<sup>2,3</sup> Post-treatment pelvic pain score on a zero to fivepoint scale, where 0 = no pain and 5 = excruciating pain

\*The basis for the **assumed risk is** the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval.

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>Unclear whether blinded, 12% attrition.

<sup>2</sup>41% dropout rate at two to four weeks.

<sup>3</sup>Wide confidence interval compatible with no effect or benefit from magnetic therapy.



#### BACKGROUND

# **Description of the condition**

The management of women with chronic pelvic pain (CPP) has for many years posed a challenge for healthcare professionals. Among women in the reproductive age group, the estimated prevalence of CPP varies widely, depending on study definitions, from 2.1% to 24% of the female population worldwide (Latthe 2006), with a notably high prevalence in the USA and the UK (14.7% and 24%, respectively) (Daniels 2010; Mathias 1996; Zondervan 1999). The reported incidence of CPP in primary care of 38 per 1000 women is comparable with the incidence of back pain (41 per 1000) and asthma (37 per 1000) (Zondervan 1999). Up to 20% of visits to gynaecologists, 40% of laparoscopies and 15% of hysterectomies in gynaecology are attributed to CPP (Gelbaya 2001; Howard 1993). At laparoscopy, a significant proportion of women with CPP (up to 55%) have no obvious pathological cause for their pain (Daniels 2009; Howard 1993). As the pathophysiology of CPP is not well understood, its treatment is often unsatisfactory and limited to symptom relief. Treatment options, ranging from conservative management to opioid analgesia and surgical intervention, vary accordingly, as do treatment outcomes (Cheong 2006). In a large proportion of women, treatment does not necessarily result in relief of pain. Thus, living with CPP carries a significant mental, social and physical burden for the sufferer, and its chronic nature puts a heavy burden on healthcare systems worldwide (Daniels 2010; Latthe 2006).

#### **Description of the intervention**

Diagnosis and treatment of CPP is complex and may be complicated by psychosocial circumstances. Non-surgical management often includes an entire concoction of treatments, such as analgesics, adjunctive agents such as anticonvulsants and antidepressants, hormonal drugs (medroxyprogesterone acetate, goserelin),  $\alpha_2$ -adrenoceptor agonists (lofexidine hydrochloride), venoconstrictor drugs (ergotamine) and venomimetics (daflon). The non-surgical approach also encompasses psychological drug interventions, which have been suggested to be beneficial in the treatment of CPP (Williams 2012). Other alternatives to medical management of CPP include psychological therapy, cognitive therapy, physiotherapy and various forms of complementary therapies (Cheong 2006). Multidisciplinary management, which is a common approach to many chronic conditions such as asthma and diabetes, still is not commonly available in gynaecology because of cost factors and the limited availability of interested specialists (Cheong 2007).

# How the intervention might work

The aetiology of chronic pelvic pain is complex. Pelvic congestion, adhesions, musculoskeletal nerve-related disorders and psychosomatic factors have been suggested as causes of CPP. Interventions targeting these factors have been used in the management of CPP.

It is suggested that pelvic pain in women can be of visceral and/or neuropathic origin. If treatment using anti-nociceptive medication (e.g. Tramadol) for visceral pain fails, second-line treatment generally consists of anti-convulsants targeting neuropathic pain (Sator-Katzenschlager 2005). Women with CPP, similar to those with other chronic pain syndromes, often have co-existing

conditions such as depression. Although anti-depressants may indirectly improve the pain experience by enhancing mood, they may also have a direct analgesic effect, as both depressive symptoms and pain are modulated by the neurotransmitters serotonin and norepinephrine (Brown 2008).

A possible vascular basis for CPP has prompted the evaluation of vasoactive agents for treatment, by analogy with cerebral migraine (Stones 2001). It has been suggested that pelvic congestion syndrome, which is responsible for CPP in a large proportion of women with no detectable organic pathology, is the result of ovarian dysfunction, and that inducing a hypooestrogenic state or antagonising the effects of oestrogens by using progesterone results in resolution of symptoms, hence the trials of medroxyprogesterone acetate versus placebo (Farquhar 1989).

Evidence suggests that up to 85% of women with CPP have dysfunction of the musculoskeletal system, including postural changes, as well as changes in the pelvic muscles, such as spasm of the levator ani (Baker 1993; Prendergast 2003). Such chronic pain caused by spasm of the pelvic floor muscles has been treated by various modalities such as local anaesthetic blockade (Langford 2007). Another technique that is being studied increasingly is the injection of type A botulinum toxin into affected muscles of the pelvic floor. This agent is thought to act selectively on the endings of cholinergic peripheral nerves, thus inhibiting the presynaptic release of acetylcholine and reducing excessive muscle tone (Gupta 2006; Thompson 2005). Other possibilities that have been explored in the treatment of high-tone dysfunction of the pelvic floor in women with CPP include transvaginal manual therapy and transvaginal electrostimulation of pelvic floor musculature. Electrical stimulation is thought to promote analgesia through the counterirritative effect that results in activation of the pain suppression system, thus offering pain relief at low cost and with few side effects (Duleba 1996).

Diagnosis and treatment of CPP is complex and may be complicated by psychosocial circumstances. Apart from medical and surgical approaches, it has been suggested that psychological treatments are helpful in reducing the frequency and severity of symptoms in all sorts of chronic pain, including unexplained pelvic pain (Williams 2012).

# Why it is important to do this review

This review is important because it will inform women with chronic pelvic pain and healthcare professionals about available evidence on management of this disease.

# **OBJECTIVES**

To assess the effectiveness and safety of non-surgical interventions for women with chronic pelvic pain.

#### **METHODS**

# Criteria for considering studies for this review

# Types of studies

We included published and unpublished randomised controlled trials (RCTs). We excluded trials that were not properly randomised. We included cross-over studies if first-phase data were valid.



#### **Types of participants**

Women with CPP, defined as intermittent or constant pain of at least three to six months' duration localised in the abdomen or pelvis, not limited to the period of menstruation or intercourse and not associated with pregnancy. We excluded studies examining specific cohorts of women known to have solely endometriosis, primary dysmenorrhoea and/or pain due to active chronic pelvic inflammatory disease.

#### Types of interventions

We considered comparisons made within the following intervention groups.

- Medical interventions versus placebo/no treatment or other types of interventions.
  - Medical interventions included interventions such as non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptive pills (OCPs), oral and non-oral progestogen, danazol, gonadotropin-releasing hormone (GnRH) analogues (alone or with 'add-back' oestrogen), progestogen-releasing intrauterine devices (IUCDs), drugs affecting blood vessels, anticholinergic drugs, antidepressants, anticonvulsants, analgesics, combined analgesic and caffeine preparations and local anaesthetic infiltration alone or in combination with corticosteroids.
- Psychological/behavioural/cognitive treatments versus no treatment/placebo/other non-surgical treatments or other types of interventions.
  - Interventions in this category included investigations for reassurance, written or oral emotional disclosures, psychotherapy, counselling, cognitive and biofeedback therapy and lifestyle interventions.
- Physical and complementary treatments versus no treatment/ sham or placebo or other types of interventions.
  - Interventions such as magnetic field therapy, therapies encompassed in traditional Chinese medicine (TCM) (acupuncture, herbal therapy, moxibustion), transcutaneous nerve stimulation and transcranial current stimulation and physical and massage therapy were considered.

# Types of outcome measures

#### **Primary outcomes**

 Effectiveness of treatment: pain measured by validated pain scales, for example, visual analogue pain scale (VAS) scores, the McGill Pain Questionnaire (MPQ), a pain improvement rating scale, general pain experience and a gynaecological pain questionnaire.

# **Secondary outcomes**

- Psychological outcomes indicated by scores such as depression scores (Hamilton Depression Rating Scale (HAM-D) score, Hospital Anxiety Depression Scale) and mood scores.
- Quality of life: indicated by, for example, the Medical Outcomes Study Short Form 36 (SF-36), the Social Adjustment Survey (SAS-WR), the Sickness Impact Profile (SIP), a general health questionnaire (GHQ), the revised Sabbatsberg Sexual Rating Scale (rSSRS) and EuroQOL-5D (EQ-5D).
- Requirement for analgesia.

 Adverse outcomes (e.g. treatment intolerance, side effects of intervention).

#### Search methods for identification of studies

We searched all published and unpublished RCTs to 5 February 2014 with no language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG)Trials Search Coordinator.

#### **Electronic searches**

We searched the following electronic databases, trial registers and websites.

- The Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials.
- The Cochrane Central Register of Controlled Trials (CENTRAL).
- MEDLINE.
- EMBASE.
- PsycINFO.
- CINAHL.

Other electronic sources of trials included the following.

- Trial registers for ongoing and registered trials (http://www.controlled-trials.com, http://clinicaltrials.gov/ct2/home, http://www.who.int/trialsearch/Default.aspx).
- Citation indexes (http://scientific.thomson.com/products/sci/).
- Conference abstracts in the Web of Knowledge (http://wokinfo.com/).
- LILACS database, for trials from the Portuguese- and Spanishspeaking world (http://bases.bireme.br/cgibin/wxislind.exe/ iah/online/?lsisScript=iah/ iah.xis&base=LILACS&lang=i&form=F).
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed/).
- OpenSIGLE database (http://opensigle.inist.fr/ and Google for grey literature).

See Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5 and Appendix 6.

#### **Searching other resources**

- We searched the citation lists of relevant publications, review articles and included studies.
- We handsearched relevant journals, abstracts and conference proceedings and several key grey literature sources.
- We personally contacted study authors to request further information, if needed.
- We approached drug/device manufacturers and experts in the field to ask for references.

# Data collection and analysis

#### **Selection of studies**

After an initial screen of titles and abstracts retrieved by the search conducted by the MDSG Trials Search Co-ordinator, the full texts of all potentially eligible studies were retrieved. Two review authors (GS and YCC) reviewed the titles and abstracts independently, examining these articles for compliance with the inclusion criteria and selecting studies eligible for inclusion in



the review. We corresponded with study investigators as required. Disagreements as to study eligibility were resolved by discussion or by a third review author (AW). The selection process has been

documented with a PRISMA flow chart Figure 1. See also Figure 2 and Figure 3.



Figure 1. Study flow diagram.

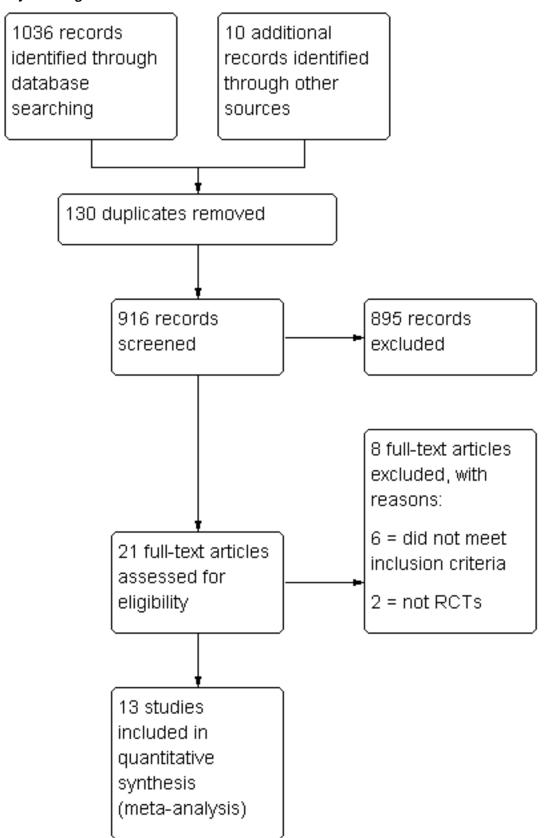




Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

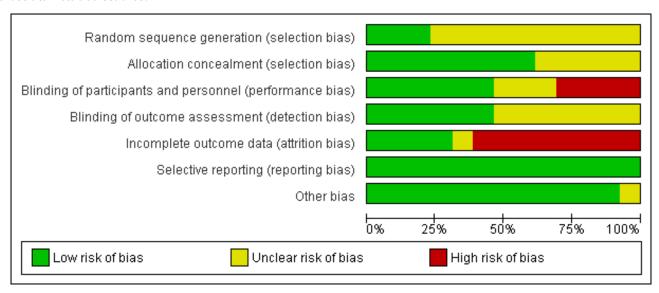




Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abbott 2006	•	•	•	?	•	•	•
Brown 2002	?	?	•	•		•	•
Engel 1998	?	?	•	•	•	•	•
Farquhar 1989	•	•	•	?	•	•	•
Ghaly 1994	?	•	?	•	?	•	•
Haugstad 2008	?	•	•	?	•	•	•
Heyman 2006	?	•	•	?	•	•	•
Norman 2004	?	?	•	•	•	•	•
Peters 1991	?	•	•	•	•	•	•
Sator-Katzenschlager 2005	?	?	•	?	•	•	?
Soysal 2001	•	•	?	•	•	•	•
Stones 2001	?	•	•	?		•	•
Walton 1992	?	?	?	?		•	



#### **Data extraction and management**

GS and YCC independently extracted the information for each included trial, using a data extraction form designed and pilot tested by the review authors. Any disagreements were resolved by discussion or by a third review author (AW). When studies had multiple publications, the main trial report was used as the reference, and additional details were derived from secondary papers. We corresponded with study investigators to request further data on methods and/or results, as required.

#### Assessment of risk of bias in included studies

Two review authors (GS and YCC) independently assessed the risk of bias of included studies. The included studies were assessed using the Cochrane risk of bias assessment tool (Version 5.1) to assess the following domains: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias. We resolved disagreements by discussion.

#### **Measures of treatment effect**

For dichotomous data, we used the numbers of events in the control and intervention groups of each study to calculate Peto odds ratios (ORs). For continuous data, we calculated the mean difference (MD) between treatment groups. We presented 95% confidence intervals (CIs) for all treatment outcomes.

#### Unit of analysis issues

No unit of analysis issues were noted, as women were the unit of randomisation.

# Dealing with missing data

Data were analysed on an intention-to-treat basis as far as possible, and attempts were made to obtain missing data from the original trialists. When these could not be obtained, only the available data were analysed. If studies reported sufficient detail for calculation of MDs but no information on associated standard deviation (SD), we planned to assume that the outcome had an SD equal to the highest SD from other studies within the same analysis.

### **Assessment of heterogeneity**

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Heterogeneity assessment was performed by measuring I<sup>2</sup>. An I<sup>2</sup> measurement greater than 50% was taken to indicate substantial heterogeneity (Higgins 2011).

#### **Assessment of reporting biases**

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we minimised their potential impact by ensuring a comprehensive search for eligible studies and duplication of data. When appropriate, we planned to use a funnel plot to assess the possibility of small-study effects. We planned to construct a funnel plot to assess potential publication bias if sufficient studies reported the same comparison.

#### **Data synthesis**

When continuous measurements were used to assess the effects of interventions, we calculated the mean difference or, alternatively, the standardised mean difference if different scales were used. We combined the data of studies that were sufficiently similar using a fixed-effect model for the following comparisons. For binary (or dichotomous) outcomes, we expressed results for each study as Peto ORs with 95% CIs. We applied a fixed-effect model to assess outcomes if heterogeneity was minor; otherwise we planned to use a random-effects Mantel-Haenszel model. We performed statistical analysis using Review Manager software (RevMan 2012). When data were skewed or SDs were not calculable, the data were entered in "Other data" tables.

- Medical interventions
  - Medical interventions versus placebo/no treatment or other interventions, specifically:
    - · Progestogen versus placebo;
    - Sertaline versus placebo; or
    - · Lofexidine versus placebo.
  - Medical interventions: head-to-head comparisons.
    - Goserelin versus progestogen.
    - · Gabapentin versus amytriptyline.
- Psychological treatments versus placebo/no treatment, or other interventions, specifically:
  - Psychotherapy versus no treatment;
  - · Ultrasound versus traditional treatment;
  - · Somatocognitive therapy versus no treatment;
  - Somatic, psychological or dietary therapy or physiotherapy versus no treatment; or
  - Written disclosure versus no treatment.
- Complementary treatments versus no treatment/sham or placebo or other interventions.
  - Magnetic field therapy versus placebo magnet.
  - Physical therapy versus standard treatment (counselling).

#### Subgroup analysis and investigation of heterogeneity

If substantial heterogeneity was noted, the review authors planned to reassess the data and perform a random-effects meta-analysis. We also planned to consider doing meta-regression analysis or subgroup analysis for the following variables.

- Intervention type.
  - o Physical therapy.
  - o Hormonal therapy.
  - Non-hormonal therapy.
  - Multi-disciplinary treatment.
- Duration of intervention: one session versus repeated sessions.
- Duration of follow-up: immediately after treatment versus posttreatment, for example, two weeks, four weeks, three months, six months, 12 months.

### Sensitivity analysis

If sufficient studies were making the same comparison, the review authors planned to conduct sensitivity analyses for the primary outcome while considering the following issues: risk of bias,



assessment of inclusion or exclusion of a study, nature of the data analysed and methods of analysis used.

# Overall quality of the body of evidence: summary of findings table

We prepared a summary of findings table using Guideline Development Tool software. This table evaluates the overall quality of the body of evidence for outcomes of pain and adverse effects, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) have been incorporated into the reporting of results for each outcome.

#### RESULTS

# **Description of studies**

#### Results of the search

The search revealed 21 studies that were potentially eligible and were retrieved in full text. A total of 13 studies met our inclusion criteria. Eight studies were excluded. See the study tables Characteristics of included studies and Characteristics of excluded studies.

#### **Included studies**

#### Study design and setting

A total of 13 RCTs were included in the review. Besides Walton 1992, which was a multicentre study, all other studies were singlecentre studies. Four were conducted in the UK, three in the USA, one in Sweden, one in the Netherlands, one in Turkey, one in Austria (Sator-Katzenschlager 2005), one in Australia (Abbott 2006) and one in Norway (Haugstad 2008).

# **Participants**

The studies included 406 women in the intervention group and 344 women in the control group.

Study populations had a similar age distribution, with mean ages of 27 to 35 years. All studies had comparable control and treatment groups with respect to parity except for Stones 2001, in which the intervention group had higher parity. All study populations had similar chronicity of pain, except in Soysal 2001, in which chronicity was not stated. All participants were women with chronic pelvic pain.

#### Interventions

- Medical interventions versus placebo/no treatment or other medical interventions (seven studies).
  - Two of seven studies compared medroxyprogesterone against placebo (Farquhar 1989; Walton 1992).
  - One of seven studies compared medroxyprogesterone versus goserelin (Soysal 2001).
  - One of seven studies compared sertraline versus placebo (Engel 1998).
  - One of seven studies compared lofexidine versus placebo (Stones 2001).
  - One of seven studies compared gabapentin versus amytriptyline versus both (Sator-Katzenschlager 2005).

- One of seven studies compared injection of botulinum toxin A versus placebo (Abbott 2006).
- Complementary treatments versus no treatment/sham or placebo or other medical interventions (two studies).
  - One of two studies compared static magnetic fields versus placebo magnets (Brown 2002).
  - One of two studies compared physical treatment (distension of painful pelvic structures) versus control (usual care with counselling) (Heyman 2006).
- Psychological/behavioural/cognitive treatments versus no treatment/placebo/other interventions (five studies).
  - One of five studies compared writing therapy (disclosure about their pain) versus control (non-disclosure) (Norman 2004).
  - One of five studies compared ultrasound scan and counselling session versus 'wait and see' (Ghaly 1994).
  - One of five studies examined an integrated approach (somatic, psychological, dietary, environmental and physiotherapeutic factors) versus standard care (Peters 1991).
  - One of five studies compared somatocognitive therapy (Mensendieck) versus standard care (Haugstad 2008).
  - One of five studies compared psychotherapy versus placebo (Farquhar 1989).

#### **Outcomes**

- · Primary outcomes.
  - 12 of 13 studies reported pain scores (e.g. VAS, MPQ, pain improvement rating scale, general pain experience, gynaecological pain questionnaire, pain beliefs and perceptions inventory (PBPI), composite pain score, Pain Disability Index) (Abbott 2006; Brown 2002; Engel 1998; Farquhar 1989; Ghaly 1994; Haugstad 2008; Heyman 2006; Norman 2004; Peters 1991; Sator-Katzenschlager 2005; Stones 2001; Walton 1992). When results are presented in dichotomous data, the improvement in pain is taken to be improvement in pain scores > 50% as defined by the studies.
- Secondary outcomes.
  - Four of 13 studies reported depression scores (e.g. HAM-D, Hospital Anxiety and Depression Scale (HADS)) (Engel 1998; Ghaly 1994; Heyman 2006; Soysal 2001).
  - Six of 13 studies reported overall effect (e.g. disturbance of daily activities, Clinical Global Impression Scale, social adjustment survey, SF-36, SIP, GHQ and EQ-5D) (Abbott 2006; Brown 2002; Engel 1998; Haugstad 2008; Norman 2004; Peters 1991).
  - Two of 13 studies checked sexual variables (e.g. rSSRS) (Heyman 2006; Soysal 2001).
  - Farquhar 1989, Sator-Katzenschlager 2005, Stones 2001 and Walton 1992 reported the side effects of treatments.

The above outcomes were reported over the following follow-up duration.

- Four weeks to two months: Brown 2002; Heyman 2006 (four weeks); Norman 2004; Stones 2001 (two months).
- Three to six months: Abbott 2006; Engel 1998; Soysal 2001; Walton 1992.



 Nine to 12 months: Farquhar 1989; Ghaly 1994; Haugstad 2008; Peters 1991.

#### **Excluded studies**

Eight studies were excluded from the review for the following reasons.

- Two of eight studies were randomised cross-over trials with no washout period (Fenton 2008;Simsek 2007).
- One of eight studies was an open-label uncontrolled trial (Brown 2008).
- One of eight studies was excluded as it was an abstract with insufficient available information (Pearce 1986).
- One of eight studies was excluded as this pilot study showed very inconsistent findings, leading the authors to not undertake analysis of outcomes (Hawk 2002).
- One of eight studies had participants entered and evaluated at different time points in control and active groups, making comparison between groups difficult (Elcombe 1997).
- One of eight studies was excluded as it included a surgical treatment (Onwude 2004).
- One of eight studies was excluded as it was not an RCT (Reginald 1987).

#### Risk of bias in included studies

#### Allocation

Five studies were at low risk of selection bias related to sequence generation, as they used computer randomisation or a random numbers table (Abbott 2006; Farquhar 1989; Norman 2004; Soysal 2001; Stones 2001). The other eight studies did not describe the method used and were at unclear risk of this bias (Brown 2002; Engel 1998; Ghaly 1994; Haugstad 2008; Heyman 2006; Peters 1991; Sator-Katzenschlager 2005; Walton 1992).

Seven studies were at low risk of selection bias related to allocation concealment (Abbott 2006; Farquhar 1989; Haugstad 2008; Norman 2004; Peters 1991; Soysal 2001; Stones 2001). The other six studies were at unclear risk of this bias (Brown 2002; Engel 1998; Ghaly 1994; Heyman 2006; Sator-Katzenschlager 2005; Walton 1992).

#### Blinding

We considered blinding to influence the findings of the outcome.

Six studies were at low risk for blinding of participants and personnel (Abbott 2006; Brown 2002; Engel 1998; Farquhar 1989; Haugstad 2008; Stones 2001). Seven studies were at low risk for blinding of outcome assessors (Abbott 2006; Brown 2002; Engel 1998; Ghaly 1994; Norman 2004; Peters 1991; Soysal 2001). Blinding was not stated in one study (Walton 1992). Blinding of participants was not fully possible in four studies (Heyman 2006; Norman 2004; Peters 1991; Sator-Katzenschlager 2005).

#### Incomplete outcome data

Four studies analysed most (> 90%) of the randomly assigned women, and we judged them as low risk (Abbott 2006; Engel 1998; Peters 1991; Soysal 2001). One had 10% loss to follow-up and was deemed to be at unclear risk (Ghaly 1994).

Eight studies were considered at high risk of attrition bias (Brown 2002; Farquhar 1989; Haugstad 2008; Heyman 2006; Norman 2004; Sator-Katzenschlager 2005; Stones 2001; Walton 1992).

#### **Selective reporting**

Protocols were available for all studies.

#### Other potential sources of bias

None were identified.

#### **Effects of interventions**

See: Summary of findings for the main comparison Medical treatment compared with placebo for the management of chronic pelvic pain; Summary of findings 2 Medical treatment of chronic pelvic pain: head-to-head comparisons; Summary of findings 3 Psychological therapy compared with control interventions for the management of chronic pelvic pain; Summary of findings 4 Complementary therapy compared with control interventions for the management of chronic pelvic pain

#### 1) Medical interventions versus placebo/no treatment

#### 1.1 Progesterone versus placebo/no treatment

#### Primary outcome: pain

# Medroxyprogesterone acetate versus placebo

Progestogen (MPA) was effective at the end of treatment, as denoted by the rate of women achieving a > 50% reduction in VAS pain score (Peto OR 3.00, 95% CI 1.70 to 5.31, two studies, n = 204, I<sup>2</sup> = 22%). Evidence of benefit was maintained up to nine months after treatment (Peto OR 2.09, 95% CI 1.18 to 3.71, two studies, n = 204, I<sup>2</sup> = 0%) (Analysis 1.1).

#### Secondary outcomes

No studies reported psychological outcomes, quality of life or requirement for analgesia.

#### Adverse outcomes

Farquhar 1989 reported a higher risk of weight gain and bloating in the MPA group than in the placebo group (weight gain 7.82, 95% CI 3.28 to 18.65, n = 85; bloatedness Peto OR 3.20, 95% CI 1.37 to 7.47, n = 85). No significant difference was noted between MPA and placebo groups in other reported medical events (e.g. leg colour change, benign breast lumps (Peto OR 1.74, 95% CI 0.52 to 5.82, n = 64)) (Walton 1992) (Analysis 1.1; Figure 4).



Figure 4. Forest plot of comparison: 1 Medical treatment versus placebo, outcome: 1.1 Progesterone versus placebo.

	Progest	•	Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events		Events		Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
1.1.1 Improvement in	-	e at en	d of treat	ment			_
Farquhar 1989 (1)	33	51	15	51	54.3%	4.07 [1.88, 8.82]	
Walton 1992	30	68	9	34	45.7%	2.10 [0.90, 4.87]	
Subtotal (95% CI)		119		85	100.0%	3.00 [1.70, 5.31]	•
Total events	63		24				
Heterogeneity: Chi²=		•		22%			
Test for overall effect:	Z = 3.78 (F	2 = 0.00	02)				
1.1.2 Improvement in	pain scor	e (up to	nine mo	onths a	fter treat	ment)	
Farquhar 1989 (2)	22	51	16	51	51.3%	1.65 [0.74, 3.66]	<del>  -</del>
Walton 1992	39	68	11	34	48.7%	2.69 [1.19, 6.11]	
Subtotal (95% CI)		119		85	100.0%	2.09 [1.18, 3.71]	•
Total events	61		27				
Heterogeneity: Chi²=				0%			
Test for overall effect:	Z = 2.53 (F	o = 0.01	)				
1.1.3 Weight gain							_
Farquhar 1989	38	45	14	40	100.0%	7.82 [3.28, 18.65]	-
Subtotal (95% CI)		45		40	100.0%	7.82 [3.28, 18.65]	•
Total events	38		14				
Heterogeneity: Not ap							
Test for overall effect:	Z = 4.64 (F	o.00	001)				
1.1.4 Bloatedness							
Farquhar 1989	29	45	14	40	100.0%	3.20 [1.37, 7.47]	-
Subtotal (95% CI)		45		40	100.0%	3.20 [1.37, 7.47]	•
Total events	29		14				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.69 (F	o = 0.00	7)				
1.1.5 Other medical e	events—le	g colou	r change	e, breas	st lumps		
Walton 1992	10	39	4	25	100.0%	1.74 [0.52, 5.82]	<del></del>
Subtotal (95% CI)		39		25	100.0%	1.74 [0.52, 5.82]	<b>◆</b>
Total events	10		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.90 (F	P = 0.37	)				
							- <del></del>
							0.005 0.1 1 10 20

- (1) 26 women in each group had psychological treatment in additiono to progestogen or placebo
- (2) 26 women in each group had psychological treatment in additiono to progestogen or placebo

#### 1.2 Lofexidine hydrochloride versus placebo

#### Primary outcome: pain

No evidence showed a significant difference between lofexidine hydrochloride and placebo in the rate of women achieving a > 50% reduction in VAS pain score (Peto OR 0.42, 95% CI 0.11 to 1.61, one study, n = 39) (Analysis 1.2).

# Secondary outcomes

No studies reported psychological outcomes, quality of life or requirement for analgesia.

#### **Adverse outcomes**

Women taking lofexidine reported significantly higher rates of dry mouth (Peto OR 8.6, 95% CI 2.44 to 30.31, one study, n=39), drowsiness (Peto OR 3.8, 95% CI 1.09 to 13.26, one study, n=39)

and dizziness (Peto OR 4.77, 95% CI 1.29 to 15.46, one study, n = 39) than women who took placebo. No significant difference between groups was noted in the incidence of headache or migraine (Peto OR 0.33, 95% CI 0.09 to 1.16, one study, n = 39) (Analysis 1.2).

#### 1.3 Sertraline versus placebo

#### Primary outcome: pain

No analysable data were available for this outcome, but one study reported no evidence of a significant difference between sertraline and placebo in pain scores on a zero to ten scale (MD -0.02, 95% CI -0.6 to -0.6, one study, n=25) (Table 1).

#### **Secondary outcomes**

# **Psychological outcomes**

No studies reported psychological outcomes.



#### Quality of life

#### Sertraline versus placebo

• No analysable data were available for this outcome, but one study reported that the SF-36 subscale for health perception (range zero to ten) showed a small but statistically significant improvement in the sertraline arm (MD 3.0, 95% CI 0.3 to 5.7, one study, n = 25), and the functioning-emotional subscale (range not specified) showed a large, statistically significant decrement in the sertraline arm (MD -30.4, 95% CI -50.3 to -10.6, one study, n = 25) (Engel 1998) (Table 1).

#### Requirement for analgesia

No studies reported this outcome.

#### **Adverse outcomes**

No studies reported this outcome.

#### 2) Medical treatment versus other medical treatment

#### 2.1 Goserelin versus progestogen

#### Primary outcome: pain

Women taking goserelin showed greater improvement in pelvic pain score at one year (as measured on a scale of one to 100) than those taking progesterone (MD 3, 95% CI 2.08 to 3.92, one study, n = 47) (Analysis 2.1).

#### **Secondary outcomes**

#### **Psychological outcomes**

Mood and sexual function were improved to a greater extent one year after treatment among women taking goserelin than among those taking progestogen (Soysal 2001) (HADS total score, MD 1.3, 95% CI 0.42 to 2.18, n = 47; rSSRS score (revised Sabbatsberg Sexual Rating scale), MD 15.5, 95% CI 11.7 to 19.23, n = 47). HADS is a self assessment mood scale that is designed specifically for use in non-psychiatric hospital outpatients to assess anxiety and depression (Zigmond 1983). The score is out of a total of 42, and the higher the score, the greater the anxiety or depression. The rSSRS is a 12-item

questionnaire of sexual functioning (Garrat 1995). A higher score (scale of zero to 100) represents greater sexual satisfaction (Analysis 2.1).

This study did not report on our other secondary outcomes (quality of life, requirement for analgesia or adverse outcomes).

#### 2.2 Gabapentin versus amytriptyline

#### Primary outcome: pain

The VAS pain score (on a one to ten scale) favoured gabapentin compared with amytriptyline at 24 months' follow-up (MD -1.50, 95% CI -2.06 to -0.94, n = 40) (Sator-Katzenschlager 2005) (Analysis 2.2).

#### **Secondary outcomes**

This study did not report on our other secondary outcomes (psychological outcomes, quality of life or requirement for analgesia).

#### Adverse outcomes

Study authors reported no significant difference in the rate of side effects among women taking gabapentin compared with women who took amytriptyline (no extractable data).

# 3) Psychological treatment versus placebo/no treatment or other interventions

#### 3.1 Improvement in pain scores

#### Primary outcome: pain

#### Ultrasound scan and counselling session versus 'wait and see'

At four to nine months' follow-up, women who had ultrasound reassurance and counselling were more likely to have improved pain than those given a 'wait and see' policy (Peto OR 6.77, 95% CI 2.83 to 16.19, n = 90) (Ghaly 1994) (Analysis 3.1; Figure 5). Assessment was based on a 40-point scale on the McGill Pain Questionnaire, with a change in score of five points deemed a meaningful improvement.



Figure 5. Forest plot of comparison: 3 Psychological therapy versus control, outcome: 3.1 Improvement in pain scores.

1.1 Utrasound scan and counselling session versus: 'wait and see' haby 1994 25 46 5 44 100.0% 6.77 [2.83, 16.19] thatoat (95% Ct) 46 5 44 100.0% 6.77 [2.83, 16.19] thatoat (95% Ct) 46 5 44 100.0% 6.77 [2.83, 16.19] thatoat (95% Ct) 46 5 44 100.0% 6.77 [2.83, 16.19] thatoat (95% Ct) 20 100.0% 3.38 [0.97, 11.80] thatoat (95% Ct) 20 20 100.0% 3.38 [0.97, 11.80] thatoat (95% Ct) 20 20 100.0% 3.38 [0.97, 11.80] thatoat (95% Ct) 20 20 100.0% 3.38 [0.97, 11.80] that events 11 5 sterogeneity. Not applicable stofro overall effect Z = 1.91 (P = 0.06)  1.3 Integrated approach (somatic, psychological, dietary, environmental and physiotherapeutic factors) versus standard care sters 1991 35 57 25 49 100.0% 1.52 [0.71, 3.27] that events 35 25 elerogeneity. Not applicable stofro overall effect Z = 1.97 (P = 0.28)  1.4 Writing therapy (disclosure of pain) versus non-disclosure proma 2004 1 6 28 20 100.0% 4.47 [1.41, 14.13] that events 16 4 20 100.0% 4.47 [1.41, 14.13] that events 16 4 28 20 100.0% 4.47 [1.41, 14.13] that events 16 4 25 100.0% 0.79 [0.24, 2.59] that events 7 8 elerogeneity. Not applicable stofro overall effect Z = 2.55 (P = 0.01)  1.5 Psychotherapy versus placebo: at end of treatment regular 1999 7 26 8 25 100.0% 0.79 [0.24, 2.59] that events 7 8 elerogeneity. Not applicable stofro overall effect Z = 0.39 (P = 0.89)  1.6 Psychotherapy versus placebo: nine months post-treatment regular 1999 7 26 8 25 100.0% 0.46 [0.14, 1.49] that events 6 10 elerogeneity. Not applicable stofro overall effect Z = 0.39 (P = 0.89)  1.6 Psychotherapy versus placebo: nine months post-treatment regular 1998 6 26 10 25 100.0% 0.46 [0.14, 1.49] that events 6 10 elerogeneity. Not applicable stofro overall effect Z = 1.29 (P = 0.20)		ychothe		Contro			Peto Odds Ratio		Peto Odds Ratio
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# Somatocognitive therapy (Mensendieck) versus standard gynaecological clinical care

Rates of improvement in pain ( $\geq$  50% reduction in VAS score) did not significantly differ between women who underwent somatocognitive therapy and those who underwent standard gynaecological treatment (Peto OR 3.38, 95% CI 0.97 to 11.80, n = 40) (Haugstad 2008) (Analysis 3.1).

# Integrated approach (somatic, psychological, dietary, environmental and physiotherapeutic factors) versus standard care

Rates of improvement in pain ( $\geq$  50% reduction in VAS score) did not significantly differ between women who underwent the integrated approach and those who underwent standard care (Peto OR 1.52, 95% CI 0.71 to 3.27, n = 106) (Peters 1991) (Analysis 3.1).

#### Writing therapy (disclosure of pain) versus non-disclosure

Rates of improvement in pain (measured on a pain scale of zero to five, with improvement considered an improvement of at least one point) showed that a significantly higher number of 'disclosure patients' improved compared with 'non-disclosure patients' (Peto OR 4.47, 95% CI 1.41 to 14.13, n = 48) (Norman 2004) (Analysis 3.1).

#### Psychotherapy versus placebo

No significant difference was noted between the psychotherapy group and the placebo group in rates of pain improvement ( $\geq$  50% reduction in VAS score) immediately after treatment (Peto OR 0.79, 95% CI 0.24 to 2.59, n = 51) or at nine months' follow-up (Peto OR 0.46, 95% 0.14 to 1.49, n = 51) (Farquhar 1989) (Analysis 3.1).

#### **Secondary outcomes**

# 3.2 Psychological outcomes

# Physiotherapy and psychotherapy versus standard gynaecological advice

Depression scores (as measured on the depression scale of the GHQ-30) did not differ significantly between women who received psychological treatment (physiotherapy and psychotherapy) and those who received standard gynaecological advice (MD -0.30, 95% CI -0.80 to 0.20, n = 26) (Haugstad 2008) (Analysis 3.2).

#### Writing therapy (disclosure of pain) versus non-disclosure

Mood at the end of two months (as measured on the negative affect scale of the Positive Affect Negative Affect Scale (PANAS)) did not differ significantly between women who underwent writing therapy



(disclosure of pain) and controls (non-disclosure) (MD -0.02, 95% CI -0.43 to 0.39, n = 48) (Norman 2004) (Analysis 3.2).

Studies of psychological treatment did not report other secondary outcomes (quality of life, requirement for analgesia or adverse effects).

# 4) Complementary treatments versus no treatment/sham or placebo or other interventions

#### Physical treatment versus standard treatment

#### Primary outcome: pain

Physical treatment (distension of painful pelvic structures) was found to be significantly better than standard treatment (counselling), as reflected by a greater reduction in self rating scores on a VAS one to 100 scale for pain intensity (MD 35.80, 95% CI 23.08 to 48.52) and for pain during intercourse (MD 19.13, 95% CI 3.61 to 34.65) (Heyman 2006) (Analysis 4.1).

#### Magnetic therapy versus placebo magnet

#### Primary outcome: pain

No evidence of benefit was found in women receiving active magnets who completed four weeks of double-blind treatment compared with those having placebo magnets in terms of the Pelvic Pain Index (MD 0.50, 95% CI -1.92 to 0.92, one study, n = 19), Clinical Global Impressions-Severity (MD -0.90, 95% CI -2.05 to 0.25, one study, n = 19) and McGill Pain Disability scores (MD -16.70, 95% CI -34.05 to 0.65, one study, n = 19) (Brown 2002) (Analysis 4.2).

Studies of physical treatment did not report secondary outcomes (quality of life, requirement for analgesia or adverse effects).

#### Other analyses

Too few studies reported the same comparison for planned subgroup and sensitivity analyses to be conducted, or for a funnel plot to be constructed.

# DISCUSSION

#### **Summary of main results**

Progestogen (MPA) was more effective than placebo at the end of treatment in terms of the number of women achieving a > 50% reduction in VAS pain score immediately after treatment (Peto OR 3.00, 95% CI 1.70 to 5.31, two studies, n = 204, I² = 22%). Evidence of benefit was maintained up to nine months after treatment (Peto OR 2.09, 95% CI 1.18 to 3.71, two studies, n = 204, I² = 0%). Women receiving medical treatment with progestogen reported more adverse effects (weight gain and bloating) than those given placebo.

Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, 95% CI 2.08 to 3.92, one study, n = 47), mood (HADS total score, MD 1.3, 95% CI 0.42 to 2.18, n = 47) and sexual function at one year than those taking progestogen (rSSRS score (revised Sabbatsberg Sexual Rating Scale), MD 15.5, 95% CI 11.7 to 19.23, n = 47). Women taking gabapentin had a more favourable VAS pain score than those taking amytriptyline (MD -1.50, 95% CI -2.06 to -0.94, n = 40). Women who underwent reassurance ultrasound scans and counselling were more likely to have improved pain than those

given a standard 'wait and see' policy (Peto OR 6.77, 95% CI 2.83 to 16.19, n = 90). Significantly more women who had writing therapy as a disclosure had improvement in pain compared with those in the non-disclosure group (MD -0.02, 95% CI -0.43 to 0.39, n = 48).

Because of the heterogeneity of the included studies, we were not able to combine the results of studies examining the effects of various forms of psychological and complementary treatment on pain and quality of life in women with CPP.

# Overall completeness and applicability of evidence

Many of the interventions were single randomised controlled studies, and this limited the available evidence on which current clinical practice can be based. Progestogen appears to be an effective treatment for chronic pelvic pain, but its efficacy beyond 12 months and in older women has not been studied. Highdose progestogen treatments are often limited by side effects and are contraindicated in women attempting to conceive. The use of neuromodulators such as gabapentin has attracted much interest, and undoubtedly, results from the feasibility study of the efficacy of action of gabapentin (Horne 2012), which is currently under way, will help shed some light on the question of whether neuromodulators are effective in the management of CPP.

We were unable to combine different treatments that involve psychological interventions to provide meaningful analysis. Although in principle, each of the interventions could be tested more rigorously in RCTs, it makes more sense in clinical terms to apply effective methods of cognitive and behavioural pain management (Williams 2012) to pelvic pain because it shares so much of the impact and problems of chronic pain at other sites (Daniels 2010).

This review is not able to conclude on the effect of non-surgical interventions on quality of life because of diversity or absence of outcome measures in the studies reviewed. It would be helpful if trialists observed the recommendations of the IMMPACT initiative on outcome measurement in pain trials (Dworkin 2005; Dworkin 2010).

# Quality of the evidence

Thirteen RCTs were included in this review. These studies included 406 women in the intervention groups and 344 women in the control groups. The conclusion of evidence of benefit drawn mainly from improvement in pain assessment scores (VAS specifically) cannot be directly translated to improvement in functional outcomes and quality of life, the latter being key contributors to the morbidity associated with chronic pelvic pain. RCTs included in this review also suffered from high attrition rates, which contributed to incomplete outcome data. A wide range of follow-up was provided (range four weeks to 12 months); studies with shorter follow-up data lend themselves to confounding effects of placebo, although studies with longer follow-up are associated with higher attrition rates

The quality of the evidence, which was rated using GRADE methods, ranged from very low to high. The main reasons for downgrading evidence quality were high attrition rates, lack of blinding, failure to clearly describe randomisation procedures and lack of precision.



#### Potential biases in the review process

Both YCC and GS independently screened and identified relevant studies; furthermore, a final search was performed at the completion of the review to ensure that no new studies had been published during preparation of the manuscript. However, despite all efforts, studies in press may have been missed.

# Agreements and disagreements with other studies or reviews

None known.

#### **AUTHORS' CONCLUSIONS**

# Implications for practice

Evidence of moderate quality supports progestogen as an option for chronic pelvic pain, with efficacy during treatment. In practice, it may be most acceptable among women unconcerned about progestogenic side effects such as weight gain and bloating. No evidence indicates that lofexidine or sertraline was more effective than placebo, although data were very scanty.

Head-to-head comparisons revealed that women taking goserelin showed greater improvement in pelvic pain score, mood and sexual function at one year compared with those taking progestogen; women taking gabapentin had a more favourable VAS pain score than those taking amytriptyline, although these results were based on single studies and therefore have to be interpreted with caution.

Women who underwent reassurance ultrasound scans and counselling were more likely to have improved pain compared with those having a standard 'wait and see' policy. Significantly more women who had writing therapy as a disclosure had improvement in pain compared with those in the non-disclosure group. Again, as these findings are based on single studies, more studies will be required to confirm the results.

The quality of the evidence was low or moderate for most comparisons, and in most cases, evidence was derived from single small studies at a high or unclear risk of bias

# Implications for research

This update of the review has shown that a wide range of interventions have been tried for the non-surgical management of chronic pelvic pain. But the fact that many of these therapies were single randomised controlled studies greatly limits the available evidence on which current clinical practice can be based. Hence, more studies are required to be replicated on these individual interventions to confirm the findings of existing studies.

Future trials should employ recommended objective and patient-reported measures that capture not just pain measures but outcome measures focused on the biopsychosocial aspects of women with CPP (Dworkin 2005; Dworkin 2010).

Future researchers in this area should consider taking advantage of advancements in technology to design studies that can capture more accurate activity and quality of life data than the limited snapshot data that questionnaires can generate.

As chronic pelvic pain has a multifactorial aetiology, shifting the research paradigm from single-intervention RCTs to those for which the main objective is to develop and deliver effective integrated multidisciplinary care pathways will be critical to the successful management of this disorder.

#### ACKNOWLEDGEMENTS

Marian Showell (Trial Search Co-ordinator of the Cochrane Menstrual Disorders and Subfertility Group) for designing and running the search. Helen Nagels and Jane Marjoribanks for methodological and editorial help.



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Abbott 2006

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# CHARACTERISTICS OF STUDIES

**Characteristics of included studies** [ordered by study ID]

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Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH. Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database.. *British Journal of Obstetrics and Gynaecology* 1999;**106**:1149-55.

ADDULL 2000								
Methods	Randomised controlled	Randomised controlled trial						
Participants	N = 60 (30 each group)							
	Women aged 18 to 55 y to their daily activities	years who had more than two years of chronic pelvic pain that caused disruption						
	Women were excluded if they were breastfeeding, pregnant or desiring pregnancy during the study period, were unwilling to use contraception during the study period or had previously received botulinum toxin type A injections to the pelvic floor. Palpable pelvic pathology, current use of aminoglycoside antibiotics, history of neurological or bleeding disorders and known sensitivity to the formulation of botu linum toxin type A were also reasons for exclusion							
Interventions	Women were randomly assigned to receive 80 units of botulinum toxin type A at a concentration of 20 units/mL or saline injections (placebo group)							
	FU 26 weeks after injections							
Outcomes	VAS, EuroQOL-5D (EQ-	VAS, EuroQOL-5D (EQ-5D), SF-12, Sexual Activities Questionnaire						
Notes								
Risk of bias								
Bias	Authors' judgement	Support for judgement						
Random sequence generation (selection bias)	Low risk Computer-generated sequence							
Allocation concealment (selection bias)	Low risk Central telephone randomisation							
Blinding of participants and personnel (perfor- mance bias)	Low risk	risk Placebo injection given						



# Abbott 2006 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% dropout  Two from placebo; one from botulinum group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Nil

# Brown 2002

Methods	Method of allocation: unclear
	Power calculation: yes
	Exclusion postrandomisation: zero
	Losses to follow-up: one
	Intention-to-treat analysis: no
	Source of funding: BIOflex Medical Magnets
Participants	Country: USA
	Number of participants: 32
	Inclusion criteria: pelvic pain > six months despite other treatment, impaired social function, trigger/circumscribed tender point on examination, normal pelvic examination, normal cervical smears
	Age: 18 to 50 years
	Source of participants: gynaecology clinic
	Exclusion criteria: pregnancy, breastfeeding, medical disorders, metal/electronic device, BMI > 35
nterventions	Treatment: static magnetic fields (n = 16)
	Control: no treatment (n = 17)
	Duration: two to four weeks
Outcomes	The McGill Pain Questionnaire, Pain Disability Index, Clinical Global Impression Scale
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified



Brown 2002 (Continued)		
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Variable duration of study. Subgroup analysis of women who continued to have four weeks of treatment showed significance. High discontinuation between two and four weeks (41% attrition rate)
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Nil

# **Engel 1998**

Methods	Randomisation: unclear
	Method of allocation: unclear
	Double-blinded
	Exclusions postrandomisation: two
	Losses to follow-up: zero
	Unusual study design: cross-over design
Participants	Country: USA
	Number of participants: 25
	Age: mean 29
	Sex: F
	Inclusion criteria: pelvic pain for longer than three months, no psychoactive medication for previous two weeks
	Exclusion criteria: laparoscopy within three months, failed seven to 10-day placebo run-in phase
Interventions	Treatments: sertaline 50 mg twice daily
	Control: placebo
	Duration: six weeks
	Follow-up: end of treatment
Outcomes	Composite pain score
	SF-36



Engel 1998 (Continued)

Hamilton Depression Rating Scale

Social Adjustment Survey

Hopkins Symptoms Checklist Somatization items

Pin

Notes

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not clearly specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	25 randomly assigned, 23 completed the study
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Nil

# Farquhar 1989

Methods	Randomisation: blocks of 12	
	Method of allocation: sealed envelopes	
	Exclusion postrandomisation: zero	
	Losses to follow-up: seven	
	Unusual study design (e.g. factorial)	
Participants	Country: England	
Participants	Country: England Number of participants: 102	
Participants		
Participants	Number of participants: 102	



Farquhar 1989 (Continued)			
(continues)	Inclusion criteria: pelvic pain for longer than six months, no pathology on laparoscopy, venogram score of five or higher		
	Exclusion criteria: recent psychiatric disease, history of thromboembolism		
	Postmenopausal, previous hysterectomy		
Interventions	Treatments: medroxyprogesterone acetate (MPA) 50 mg daily (n = 25)		
	MPA and psychotherap	y (n = 26)	
	Control: placebo (n = 2	5)	
	Placebo and psychotherapy (n = 26)		
	Duration: four months		
	Follow-up: nine months		
Outcomes	Visual analogue scale p	pain score	
	Pain improvement rati	ng scale	
	Side effects		
Notes	Not blinded to psychotherapy. Quality score A		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Randomisation by random numbers table	
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes for medications	
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Double-blinded	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was recognised that the women might know whether they were receiving MPA because of its effect on their menstrual cycle. Therefore, all were told that both treatments— MPA and placebo—could induce amenorrhoea or irregular vaginal bleeding or have no obvious effect. In addition, women were asked to stop all forms of hormonal or intrauterine contraception and to use barrier methods throughout the 13 months of the trial	
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 102 women, 84 completed the full study (18% attrition). Of the other 18 women, 12 withdrew during the treatment period and six during the follow-up. Reasons cited were pregnancy, failure to attend the clinic and inability to maintain trial protocol	
Selective reporting (reporting bias)	Low risk	Less than 10% loss to follow-up	
Other bias	Low risk	Nil	



GI	nal	w	1	9	9	4

Methods	Closed envelope system		
	Losses to follow-up: 10		
Participants	Country: Scotland		
	Number of participants: 100 (50 each group)		
	Age: 21 to 55		
	Sex: F		
	Inclusion criteria: > six months' pain, negative laparoscopy  Exclusion criteria: previous malignant disease, mental retardation, medical treatment for pelvic pain a first visit, suspicion of malignant disease on pelvic examination, abnormal pelvic examination		
Interventions	Treatments: US scan and education/counselling sessions		
	Control: 'wait and see' policy (standard treatment)		
	Duration: four to nine months' reassessment		
Outcomes	McGill Pain Scale score: at least five-point improvement		
	Hospital Anxiety Depression Scale: improvement in category (normal, borderline, depressed)		

# Risk of bias

Notes

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified, quote: 'random allocation to groups'
Allocation concealment (selection bias)	Low risk	Closed envelope system
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	Not possible because of the nature of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessed blind to allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of 100 randomly assigned, 10 failed to attend for follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Nil



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Methods	Randomised trial	
Participants	Women between the ages of 20 and 50 years with deep pelvic pain lasting between one and 10 years	
Interventions	Treatment group received 10 treatment sessions with the Mensendieck therapist (Haugstad 2007) of one hour's duration over 90 days, and the control group received standard gynaecological advice at inclusion and again during the treatment period. This therapeutic approach can be seen as a mixture of physiotherapy and psychotherapy. It teaches patients to change their posture, breathing patterns and the way they move to reduce their pain. It uses a cognitive approach to allow women to have an improved understanding and experience of their body  Treatment period: three months  FU: one year  16 study groups, 18 controls	
Outcomes	VAS, GHQ-30	

# Notes

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Randomisation occurred by drawing a folded piece of paper with the participant's name from a jar, thus allocating the name to a previously chosen treatment group. Randomisation was performed by a person external to the study
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Not possible in this case, unclear whether assessors blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No attrition figures stated, but at one year, only 13 women in each group had completed the questionnaires
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Nil

# Heyman 2006

Methods Allocation concealment: sealed envelope system, blocks of four (balanced)

Blinding: no



Н	leyma	n 200	6 (Continued)
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Exclusion postrandomisation: zero

Losses to follow-up: five (three/two)

Power calculation: yes

Intention-to-treat analysis: none

**Participants** 

Country: Sweden

No. of participants: 50 (25 each group)

Age: median 33 (19 to 54)

Sex: F

Inclusion criteria: pelvic pain in fertile women > 19 years of age with a duration of at least six months,

continuous or intermittent pain at least two days/wk

Exclusion criteria: known disease of abdomen, pelvis or lumbar spine; pregnancy; STI; severe mental illness; substance abuse; previous treatment with distension of painful structures in the pelvic floor

Interventions

Treatment: The participant lay in a prone position; the physician placed his index finger deep into the participant's rectum, and previously identified painful structures were treated in the following order: At a point two finger-widths lateral of the sacrum, the physician used his index finger to exert strong pressure against the sacrotuberous/spinal ligaments for 15 s to elicit pain. Thereafter, the musculature of the pelvic floor and the joint between the coccyx and the sacrum were concurrently forcefully distended dorsally for 60 s with the index finger. This procedure was repeated after two to three weeks

Control: standard care (counselling)

Duration: four to six weeks

Outcomes

VAS

Notes

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated
Allocation concealment (selection bias)	Low risk	By drawing an envelope, assignment to treatment or control group was performed in blocks of four (i.e. the number of participants in each group was balanced after each fourth participant)
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Blinding not possible, unclear whether assessors blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Three of 25 (> 10%) dropped out from each group



Heyman 2006 (Continued)				
Selective reporting (reporting bias)	Low risk	All outcomes reported		
Other bias	Low risk	Nil		

# Norman 2004

Methods	Method of allocation: randomly assigned in blocks of two			
	Power calculation: no			
	Intention-to-treat analysis: no			
Participants	Country: United States			
	Number of participants: 48 (28 disclosure, 20 control)			
	Age: 18 to 64			
	Sex: F			
Interventions	Treatments: Two groups of women wrote about their positive (control group) and their negative (disclosure group) experience of pain and had their health status assessed at the end of two months			
Outcomes	McGill Pain Questionnaire			
Notes				

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised in blocks of 2' into sealed packets
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: 'interviewer was blind to group assignment'
Incomplete outcome data (attrition bias) All outcomes	High risk	60 randomly assigned, 12 dropped out (four intervention, eight control group). Reasons obtained; > 10% attrition
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Nil



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Methods	Methods of allocation: sealed envelope				
	Outcome assessor blind to allocation				
	Losses to follow-up: six unsuitable for laparoscopy				
Participants	Country: Netherlands				
	Participants: 106 (57 treatment, 49 control)				
	Age: 16 to 58				
	Sex: F				
	Inclusion criteria: chronic pelvic pain > three months, no problem with Dutch, no mental retardation				
	Exclusion criteria: no malignancy/disease requiring prompt gynaecological intervention, no history of psychiatric/psychotherapeutic treatment for abdominal pain, no elaborate medical analysis re abdominal pain in the past two years				
Interventions	Treatment: integrated (guided by pain model by Loeser 1980, which comprises four components: nociception, pain sensation, pain suffering and pain behaviour; equal attention was devoted to possible organic, psychological, dietary and environmental causes of pain)				
	Control: standard treatment (includes laparoscopy)				
	Duration of treatment: six months				
	Follow-up: one year				
Outcomes	General pain experience				
	Disturbance of daily activities				
	Associated symptoms				
	McGill VAS score				
N. I					

# Notes

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Quote: 'randomisation was done by means of closed envelope procedure'
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Blinding not possible, but unclear whether assessors blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blind to allocation



Peters 1991 (Continued)						
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts				
Selective reporting (reporting bias)	Low risk	All outcomes reported				
Other bias	Low risk	Nil				

## Sator-Katzenschlager 2005

Methods	Randomisation methods not specified
Participants	CPP longer than six months
Interventions	Gabapentin (n = 20), amytriptyline (n = 20) or combination (n = 16)
	Dose of amytriptyline was increased from an initial dose of 25 mg per day up to a maximum dose of 150 mg per day in 25-mg increments each week until sufficient pain relief or the occurrence of side effects such as somnolence, dizziness, orthostatic hypotension, palpitations, dry mouth and weight gain. The dose of gabapentin was increased from 300 mg per day up to a maximum dose of 3600 mg per day in 300-mg increments each week until sufficient pain relief or the occurrence of side effects
Outcomes	VAS
Notes	

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Not blinded as open-label trial, unclear whether assessors blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven participants dropped out because of side effects; > 10% dropout
Selective reporting (reporting bias)	Low risk	All outcomes reported



## Sator-Katzenschlager 2005 (Continued)

Other bias Unclear risk

Seven participants excluded after randomisation, so not analysed by intention-to-treat, but same number of dropouts from gabapentin (three) or amytriptyline group (three)

## Soysal 2001

Methods	Method of allocation: computer-generated numbered opaque sealed envelopes
Participants	Country: Turkey
	47 women with pelvic pain and venographically demonstrated pelvic congestion
Interventions	Goserelin 3.6 mg subcutaneous implant monthly for six months versus medroxyprogesterone acetate tablets 30 mg daily for six months
Outcomes	Venography score; pelvic symptom and physical examination score (modified from Biberoglu and Behrman); Hospital Anxiety, Depression and Total scores; revised Sabbatsberg Sexual Rating Scale
Notes	Note: NO dropouts

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	Blinding: some outcomes assessed double-blind. Participants not blind owing to modes of drug administration
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At final assessment of periuterine venography, operators were blinded
Incomplete outcome data	Low risk	Exclusion postrandomisation: zero
(attrition bias) All outcomes		Losses to follow-up: zero
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Nil

## Stones 2001

Methods Sealed envelope system. Double-blinded

Power calculation: yes



Stones 2001 (Continued)	Number of participants	s randomly assigned: 39			
Participants	Country: England				
	Number of participants	s: 39			
	Age: 25 to 35				
	Sex: F				
	Inclusion criteria: pelvi	c pain > six months, laparoscopy identified no pathology			
	Exclusion criteria: hyst	erectomised women			
Interventions	Treatment: lofexidine 2	200 mcg twice daily, increasing to 600 mcg twice daily (first three weeks)			
	Control: placebo table	ts			
	Duration: eight weeks				
	Follow-up: until the en	d of treatment			
Outcomes	Visual analogue scale pain score. Participant's self rating of pain as worst, unchanged, somewhat relieved, considerably relieved or completely relieved				
Notes	Note high dropout rate in treatment group (nine of 19 completed eight weeks of treatment)				
Risk of bias					
Bias	Authors' judgement	Support for judgement			
Random sequence generation (selection bias)	Unclear risk	Quote: "Women were randomised using a sealed envelope system to receive lofexidine hydrochloride or placebo"			
Allocation concealment (selection bias)	Low risk	Sealed envelope			
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Double-blinded, unclear whether assessors blinded			
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated			
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate, > 10% dropout			
Selective reporting (reporting bias)	Low risk	All outcomes reported			
Other bias	Low risk	Nil			

## Walton 1992

Methods Methods of allocation: not stated.



mance bias) All outcomes

All outcomes

(attrition bias)

All outcomes

porting bias)

Blinding of outcome as-

sessment (detection bias)

Incomplete outcome data

Selective reporting (re-

Walton 1992 (Continued)					
	Blinding: not stated				
	Exclusion postrandom	isation: zero			
Participants	Country: UK				
	Number of participants	s: 165			
	Age: not given				
	Sex: F				
	Inclusion criteria: pelvi	c pain for longer than six months			
	No pathology on lapare	oscopy			
	Exclusion criteria not g	iven			
Interventions	Treatment: medroxypr	ogesterone acetate 50 mg daily			
	Control: placebo tablets				
	Duration: four months				
	Follow-up: only until end of treatment				
Outcomes	Visual analogue scale p	pain score			
	Pain improvement rati	ng: better/not better			
Notes	Note very high dropout rate in MPA and placebo groups. Published report does not give SD for mean VAS, so data entered in Table are the numbers reporting 50% reduction in VAS at completion of the study. This allowed comparison with Farquhar 1989, as the drug, dose and duration of therapy are the same. Complete study report obtained by the review authors				
Risk of bias					
Bias	Authors' judgement	Support for judgement			
Random sequence generation (selection bias)	Unclear risk	Quote: "Two patients were allocated, at random, to the treatment group for each one given placebo"			
Allocation concealment (selection bias)	Unclear risk	Not stated			
Blinding of participants and personnel (perfor-	Unclear risk	Not stated			

Not stated

completed the study

All outcomes reported

High dropout rate, reasons obtained; commonest is non-compliance; losses

to follow-up: 64% of those taking active drug and 57% of those taking placebo

Unclear risk

High risk

Low risk



Walton 1992 (Continued)

Other bias Low risk Nil

# **Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Brown 2008	Open-label trial. Lack of placebo control group, lack of randomisation
Elcombe 1997	Participants entered and evaluated at different time points in control and active groups, making comparison between groups difficult
Fenton 2008	Cross-over trial with no washout period
Onwude 2004	Includes surgery
Pearce 1986	Abstract only. No data available
Reginald 1987	Not an RCT
Simsek 2007	Randomised cross-over trial without washout period

# **Characteristics of studies awaiting assessment** [ordered by study ID]

## Horne 2012

Methods	Randomised controlled trial (pilot feasibility study)
Participants	n = 60 women recruited from NHS UK hospital
Interventions	Women randomly assigned to gabapentin versus placebo
Outcomes	Primary objective is to assess recruitment and retention rates. Secondary objectives are to determine the effectiveness and acceptability to participants of proposed methods of recruitment and randomisation, drug treatments and assessment tools and to perform a pretrial cost-effectiveness assessment of treatment with gabapentin
Notes	

# DATA AND ANALYSES

# Comparison 1. Medical treatment versus placebo

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Progesterone versus place- bo	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

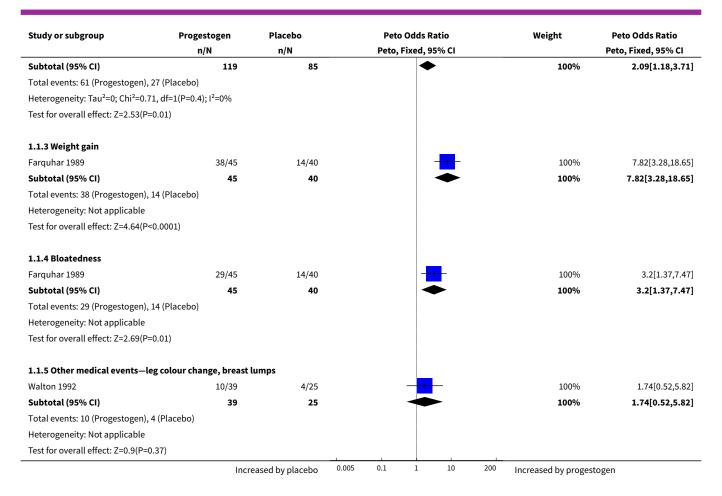


Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 Improvement in pain score at end of treatment	2	204	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.00 [1.70, 5.31]
1.2 Improvement in pain score (up to nine months after treatment)	2	204	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.09 [1.18, 3.71]
1.3 Weight gain	1	85	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.82 [3.28, 18.65]
1.4 Bloatedness	1	85	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.20 [1.37, 7.47]
1.5 Other medical events— leg colour change, breast lumps	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.52, 5.82]
2 Lofexidine versus placebo	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Improvement in pain score	1	39	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.11, 1.61]
2.2 Drowsiness/lethargy	1	39	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.80 [1.09, 13.26]
2.3 Dry mouth	1	39	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.60 [2.44, 30.31]
2.4 Dizziness	1	39	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.47 [1.29, 15.46]
2.5 Headache/migraine	1	39	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.09, 1.16]

Analysis 1.1. Comparison 1 Medical treatment versus placebo, Outcome 1 Progesterone versus placebo.

Study or subgroup	Progestogen	Placebo	Pete	Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI			Peto, Fixed, 95% CI
1.1.1 Improvement in pain	score at end of treatment					
Farquhar 1989	33/51	15/51		-	54.27%	4.07[1.88,8.82]
Walton 1992	30/68	9/34		-	45.73%	2.1[0.9,4.87]
Subtotal (95% CI)	119	85		•	100%	3[1.7,5.31]
Total events: 63 (Progestoger	n), 24 (Placebo)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =	1.29, df=1(P=0.26); I <sup>2</sup> =22.42%					
Test for overall effect: Z=3.78	(P=0)					
1.1.2 Improvement in pain	score (up to nine months aft	er treatment)				
Farquhar 1989	22/51	16/51		+	51.27%	1.65[0.74,3.66]
Walton 1992	39/68	11/34	1	<del></del>	48.73%	2.69[1.19,6.11]
	Incre	eased by placebo	0.005 0.1	1 10	200 Increased by progest	ogen

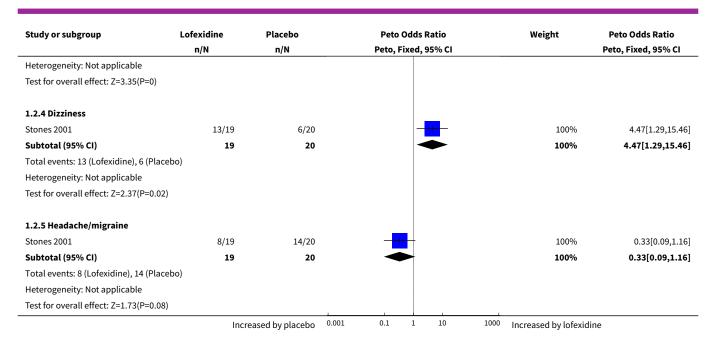




Analysis 1.2. Comparison 1 Medical treatment versus placebo, Outcome 2 Lofexidine versus placebo.

Study or subgroup	Lofexidine	Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
1.2.1 Improvement in pain score					
Stones 2001	4/19	8/20	<del>-</del>	100%	0.42[0.11,1.61]
Subtotal (95% CI)	19	20		100%	0.42[0.11,1.61]
Total events: 4 (Lofexidine), 8 (Placebo)	)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
1.2.2 Drowsiness/lethargy					
Stones 2001	14/19	8/20	<del></del>	100%	3.8[1.09,13.26]
Subtotal (95% CI)	19	20	<b>—</b>	100%	3.8[1.09,13.26]
Total events: 14 (Lofexidine), 8 (Placebo	o)				
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
1.2.3 Dry mouth					
Stones 2001	13/19	3/20	<del>-</del>	100%	8.6[2.44,30.31]
Subtotal (95% CI)	19	20		100%	8.6[2.44,30.31]
Total events: 13 (Lofexidine), 3 (Placebo	o)				
	Incre	eased by placebo	0.001 0.1 1 10 10	1000 Increased by lofexidir	ne





## Comparison 2. Medical treatment: head-to-head comparison

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Goserelin versus progestogen	1		Mean Difference (IV, Fixed, 95% CI)	Totals not select- ed
1.1 Improvement in pelvic pain score at one year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 rSSRS score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 HADS total score at one year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Gabapentin versus amytripty- line	1		Mean Difference (IV, Fixed, 95% CI)	Totals not select- ed
2.1 VAS pain score at 24 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Medical treatment: head-to-head comparison, Outcome 1 Goserelin versus progestogen.

Study or subgroup	G	oserelin	Pr	ogestagen		Mea	n Differen	ce		Mean Difference
	N	Mean(SD)	N	Mean(SD)		Fix	ced, 95% C	I		Fixed, 95% CI
2.1.1 Improvement in pelvio	pain score at on	e year								
Soysal 2001	23	7.7 (1.8)	24	4.7 (1.4)			+			3[2.08,3.92]
2.1.2 rSSRS score										
Soysal 2001	23	62.5 (5)	24	47 (7.8)				-		15.5[11.77,19.23]
					1	1				
			Increase	ed by progestagen	-20	-10	0	10	20	Increased by goserelin



Study or subgroup	Goserelin		Pr	Progestagen		Mean Difference				Mean Difference
	N	Mean(SD)	N	Mean(SD)		Fi	xed, 95% (	CI		Fixed, 95% CI
2.1.3 HADS total score at one year										
Soysal 2001	23	4.6 (1.1)	24	3.3 (1.9)	1		+			1.3[0.42,2.18]
			Increase	ed by progestagen	-20	-10	0	10	20	Increased by goserelin

# Analysis 2.2. Comparison 2 Medical treatment: head-to-head comparison, Outcome 2 Gabapentin versus amytriptyline.

Study or subgroup	Gal	bapentin	Am	ytriptyline	Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
2.2.1 VAS pain score at 24 mont	hs					
Sator-Katzenschlager 2005	20	1.9 (0.9)	20	3.4 (0.9)	+	-1.5[-2.06,-0.94]
			Fa	vours Gabanentin	-5 -2.5 0 2.5 5	Favours Amytriptyline

# Comparison 3. Psychological therapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in pain scores	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Ultrasound scan and counselling session versus 'wait and see'	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.77 [2.83, 16.19]
1.2 Somatocognitive therapy (Mensendieck) versus standard gynaeco- logical clinical care	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [0.97, 11.80]
1.3 Integrated approach (somatic, psychological, dietary, environmental and physiotherapeutic factors) versus standard care	1	106	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.71, 3.27]
1.4 Writing therapy (disclosure of pain) versus non-disclosure	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.47 [1.41, 14.13]
1.5 Psychotherapy versus placebo: at end of treatment	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.24, 2.59]
1.6 Psychotherapy versus placebo: nine months post-treatment	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.14, 1.49]
2 Depression/negative mood scores	2		Mean Difference (IV, Fixed, 95% CI)	Totals not select- ed
2.1 Physiotherapy and psychotherapy versus standard gynaecological advice	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Writing therapy (disclosure of pain) versus non-disclosure	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
	1			0.0 [0.0, 0.0]



Analysis 3.1. Comparison 3 Psychological therapy versus control, Outcome 1 Improvement in pain scores.

Study or subgroup	Psychotherapy	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
3.1.1 Ultrasound scan and counsel	lling session versus 'w	ait and see'			
Ghaly 1994	25/46	5/44	-	100%	6.77[2.83,16.19]
Subtotal (95% CI)	46	44	•	100%	6.77[2.83,16.19]
Total events: 25 (Psychotherapy), 5	(Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=4.3(P<0.000	01)				
3.1.2 Somatocognitive therapy (M cological clinical care	ensendieck) versus st	andard gynae-			
Haugstad 2008	11/20	5/20	<b>—</b>	100%	3.38[0.97,11.8]
Subtotal (95% CI)	20	20		100%	3.38[0.97,11.8]
Total events: 11 (Psychotherapy), 5					,,
Heterogeneity: Not applicable	(				
Test for overall effect: Z=1.91(P=0.06	5)				
3.1.3 Integrated approach (somatimental and physiotherapeutic fac					
Peters 1991	35/57	25/49	-	100%	1.52[0.71,3.27]
Subtotal (95% CI)	57	49	<b>→</b>	100%	1.52[0.71,3.27]
Total events: 35 (Psychotherapy), 25	(Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.07(P=0.28	3)				
3.1.4 Writing therapy (disclosure o	of pain) versus non-dis	closure			
Norman 2004	16/28	4/20	<del>-   -  </del>	100%	4.47[1.41,14.13]
Subtotal (95% CI)	28	20	<b>—</b>	100%	4.47[1.41,14.13]
Total events: 16 (Psychotherapy), 4	(Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=2.55(P=0.01	1)				
3.1.5 Psychotherapy versus placel	bo: at end of treatmen	t			
Farquhar 1989	7/26	8/25	<del></del>	100%	0.79[0.24,2.59]
Subtotal (95% CI)	26	25	<b>*</b>	100%	0.79[0.24,2.59]
Total events: 7 (Psychotherapy), 8 (0	Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.69	9)				
3.1.6 Psychotherapy versus placel	bo: nine months post-t	reatment			
Farquhar 1989	6/26	10/25	<del></del>	100%	0.46[0.14,1.49]
Subtotal (95% CI)	26	25		100%	0.46[0.14,1.49]
Total events: 6 (Psychotherapy), 10	(Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.29(P=0.2)					



# Analysis 3.2. Comparison 3 Psychological therapy versus control, Outcome 2 Depression/negative mood scores.

Study or subgroup	Psycholog	gical treatment	No	treatment		Mean Difference	•	Mean Difference
	N	Mean(SD)	N	Mean(SD)		Fixed, 95% CI		Fixed, 95% CI
3.2.1 Physiotherapy and ps	sychotherapy versi	us standard gynaed	cological a	dvice				
Haugstad 2008	13	2.6 (0.7)	13	2.9 (0.6)		-+-		-0.3[-0.8,0.2]
3.2.2 Writing therapy (disc	losure of pain) vers	sus non-disclosure						
Norman 2004	28	2.1 (0.6)	20	2.1 (0.8)		. —		-0.02[-0.43,0.39]
			Favours	s psych treatment	-2	-1 0	1 2	Favours control

## Comparison 4. Complementary therapy versus control

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Distension of painful pelvic structures versus counselling	1		Mean Difference (IV, Fixed, 95% CI)	Totals not select- ed
1.1 Intensity of pelvic pain: change in pain score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Painful intercourse: change in pain score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Magnetic therapy versus control magnet	1		Mean Difference (IV, Fixed, 95% CI)	Totals not select- ed
2.1 Pelvic Pain Index	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Clinical Global Impression-Severity	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Pain Disability Index	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

# Analysis 4.1. Comparison 4 Complementary therapy versus control, Outcome 1 Distension of painful pelvic structures versus counselling.

Study or subgroup	Phys	Physical therapy		Control		Mean Difference			Mean Difference	
	N	Mean(SD)	N	Mean(SD)		Fix	ced, 95%	CI		Fixed, 95% CI
4.1.1 Intensity of pelvic pair	n: change in pain	score								
Heyman 2006	25	35 (31)	23	-0.8 (9.2)						35.8[23.08,48.52]
4.1.2 Painful intercourse: cl	hange in pain sco	re								
Heyman 2006	25	19 (38)	23	-0.1 (10.7)		1		_		19.13[3.61,34.65]
				Favours control	-100	-50	0	50	100	Favours physical therapy



# Analysis 4.2. Comparison 4 Complementary therapy versus control, Outcome 2 Magnetic therapy versus control magnet.

Study or subgroup	Magı	netic therapy	Con	trol magnet	N	Aean Differe	nce		Mean Difference
	N	Mean(SD)	N	Mean(SD)		Fixed, 95%	CI		Fixed, 95% CI
4.2.1 Pelvic Pain Index									
Brown 2002	8	2.5 (1.6)	11	3 (1.5)		+			-0.5[-1.92,0.92]
4.2.2 Clinical Global Impression	n-Severity								
Brown 2002	8	3.3 (1.3)	11	4.2 (1.2)		+			-0.9[-2.05,0.25]
4.2.3 Pain Disability Index									
Brown 2002	8	23.5 (20.6)	11	40.2 (16.7)					-16.7[-34.05,0.65]
			Favours	magnetic therapy	-40 -20	0	20	40	Favours control

#### **ADDITIONAL TABLES**

#### Table 1. Change in pain, depression, somatisation and functional status

Engel 1998		
Composite pain intensity	SF-36 functioning-emotional subscale	Health perception
-0.02, 95% CI -0.6 to 0.6	-30.4, 95% CI -50.3 to -10.6	3.0, 95% CI 0.3 to 5.7

#### **APPENDICES**

## **Appendix 1. Ovid MEDLINE**

- 1 exp Life Style/ (55316)
- 2 exp exercise/ or exp exercise therapy/ or exp relaxation techniques/ or exp walking/ or exp yoga/ (119058)
- 3 Life Style\$.tw. (8185)
- 4 exercis\$.tw. (172356)
- 5 (walk\$ or jog or run or yoga).tw. (108651)
- 6 exp Diet/ (169662)
- 7 diet\$.tw. (334694)
- 8 (treatment\$ or therap\$).tw. (3515613)
- 9 exp psychology/ or exp cognitive science/ or exp psychology, medical/ (55140)
- 10 psycholog\$.tw. (141613)
- 11 (cognitive adj5 therap\$).tw. (9657)
- 12 psychotherap\$.tw. (28610)
- 13 meditation.tw. (1882)
- 14 (biofeedback or hypnosis or reassur\$).tw. (17256)
- 15 ultraso\$.tw. (213950)
- 16 exp analgesics/ or exp clonidine/ or exp analgesics, non-narcotic/ or exp anti-inflammatory agents, non-steroidal/ or exp diclofenac/ or exp ibuprofen/ or exp naproxen/ or exp cyclooxygenase inhibitors/ (398830)
- 17 non-steroidal anti-inflammator\$.tw. (9925)
- 18 NSAIDS.tw. (11889)
- 19 exp Contraceptives, Oral/ (39927)
- 20 (oral contracept\$ or OCP).tw. (22244)
- 21 exp Progestins/ (58187)
- 22 (progestin\$ or progestogen\$).tw. (13525)
- 23 (danazol or GnRH analogue\$).tw. (3231)



24 exp Antidepressive Agents/ (112330)

25 Antidepress\$.tw. (41592)

26 anticonvuls\$.tw. (18010)

27 analges\$.tw. (77720)

28 caffeine.tw. (20048)

29 local anaesth\$.tw. (9304)

30 corticosteroid\$.tw. (67567)

31 (counselling or counseling).tw. (50580)

32 iucd.tw. (414)

33 transcutaneous nerve stimulation.tw. (248)

34 exp complementary therapies/ or exp acupressure/ or exp acupuncture therapy/ or exp electroacupuncture/ or exp moxibustion/ or exp holistic health/ or exp medicine, traditional/ or exp mind-body therapies/ or exp "biofeedback (psychology)"/ or exp hypnosis/ or exp "imagery (psychotherapy)"/ or exp meditation/ or exp relaxation therapy/ or exp yoga/ or exp phytotherapy/ or exp reflexotherapy/ (157318)

35 exp anesthetics, local/ or exp lidocaine/ (84838)

36 local anesthetic\$.tw. (12217)

37 referral\$.tw. (56399)

38 magnetic field\$.tw. (22048)

39 sertraline.tw. (2747)

40 medroxyprogesterone\$.tw. (5030)

41 emotional disclosure.tw. (102)

42 reinforcement.tw. (20607)

43 goserelin.tw. (696)

44 dihydroergotamine.tw. (1274)

45 lofexidine.tw. (146)

46 (chinese medicine\$ or chinese herb\$).tw. (12418)

47 pain relief.tw. (18775)

48 gonadotropin-releasing hormone analogue\$.tw. (367)

49 or/1-48 (5112093)

50 exp Pelvic Pain/ (5690)

51 (Pelv\$ adj1 Pain\$).tw. (5141)

52 (Pelv\$ adj1 congest\$).tw. (203)

53 abdomin\$ pain\$.tw. (31974)

54 or/50-53 (40525)

55 49 and 54 (22265)

56 randomized controlled trial.pt. (322734)

57 controlled clinical trial.pt. (83763)

58 randomized.ab. (238641)

59 placebo.tw. (137933)

60 clinical trials as topic.sh. (158570)

61 randomly.ab. (175416)

62 trial.ti. (102055)

63 (crossover or cross-over or cross over).tw. (52722)

64 or/56-63 (791047)

65 (animals not (humans and animals)).sh. (3594930)

66 64 not 65 (730147)

67 66 and 55 (2640)

68 (200909\$ or 200910\$ or 200911\$ or 200912\$).ed. (242918)

69 (2011\$ or 2012\$).ed. (1175160)

70 68 or 69 (1418078)

71 67 and 70 (293)

This search was updated on 15 May 2013, and again on 5 February 2014.

## **Appendix 2. PsycINFO**

1 (Pelv\$ adj1 Pain\$).tw. (344)

2 (Pelv\$ adj1 congest\$).tw. (7)

3 1 or 2 (348)

4 random.tw. (34819)

5 control.tw. (271098)

6 double-blind.tw. (15805)



7 clinical trials/ (5895) 8 placebo/ (3166) 9 exp Treatment/ (511206) 10 or/4-9 (774043) 11 3 and 10 (158) 12 limit 11 to yr="2009 -Current" (37)

This search was updated on 15 May 2013, and again on 5 February 2014.

### **Appendix 3. EMBASE**

- 1 Life Style\$.tw. (10557)
- 2 exercis\$.tw. (206770)
- 3 (walk\$ or jog or run or yoga).tw. (129681)
- 4 exp Diet/ (162989)
- 5 diet\$.tw. (385363)
- 6 psycholog\$.tw. (200082)
- 7 (cognitive adj5 therap\$).tw. (14563)
- 8 psychotherap\$.tw. (40897)
- 9 meditation.tw. (2356)
- 10 (biofeedback or hypnosis or reassur\$).tw. (21541)
- 11 ultraso\$.tw. (269667)
- 12 non-steroidal anti-inflammator\$.tw. (12612)
- 13 NSAIDS.tw. (16871)
- 14 (oral contracept\$ or OCP).tw. (22315)
- 15 (progestin\$ or progestogen\$).tw. (14259)
- 16 (danazol or GnRH analogue\$).tw. (4102)
- 17 Antidepress\$.tw. (55468)
- 18 anticonvuls\$.tw. (22015)
- 19 analges\$.tw. (98950)
- 20 caffeine.tw. (23068)
- 21 local anaesth\$.tw. (11695)
- 22 corticosteroid\$.tw. (84150)
- 23 (counselling or counseling).tw. (62272)
- 24 iucd.tw. (464)
- 25 transcutaneous nerve stimulation.tw. (286)
- 26 local anesthetic\$.tw. (14301)
- 27 referral\$.tw. (71060)
- 28 magnetic field\$.tw. (19054)
- 29 sertraline.tw. (3769)
- 30 medroxyprogesterone\$.tw. (5409)
- 31 emotional disclosure.tw. (132)
- 32 reinforcement.tw. (21250)
- 33 goserelin.tw. (937)
- 34 dihydroergotamine.tw. (1486)
- 35 lofexidine.tw. (195)
- 36 (chinese medicine\$ or chinese herb\$).tw. (17182)
- 37 pain relief.tw. (25378)
- 38 gonadotropin-releasing hormone analogue\$.tw. (435)
- 39 nerve block.tw. (4772)
- 40 exp nerve block/ (21291)
- 41 exp lifestyle/ (59627)
- 42 exp exercise/ (169176)
- 43 exp psychology/ (143266)
- 44 exp analgesic agent/ (555528)
- 45 exp nonsteroid antiinflammatory agent/ (370296)
- 46 exp oral contraceptive agent/ (48771)
- 47 exp antidepressant agent/ (270421)
- 48 exp gestagen/ (126786)
- 49 exp alternative medicine/ (29258)
- 50 exp local anesthetic agent/ (158486)
- 51 or/1-50 (2794136)



- 52 Pelv\$ Pain\$.tw. (6765)
- 53 Pelv\$ congest\$.tw. (252)
- 54 abdomin\$ pain\$.tw. (42822)
- 55 exp pelvis pain syndrome/ (8090)
- 56 CPP.tw. (6602)
- 57 or/52-56 (58811)
- 58 Clinical Trial/ (862803)
- 59 Randomized Controlled Trial/ (318508)
- 60 exp randomization/ (57568)
- 61 Single Blind Procedure/ (15595)
- 62 Double Blind Procedure/ (107813)
- 63 Crossover Procedure/ (33346)
- 64 Placebo/ (194847)
- 65 Randomi?ed controlled trial\$.tw. (72598)
- 66 Rct.tw. (8838)
- 67 random allocation.tw. (1124)
- 68 randomly allocated.tw. (16791)
- 69 allocated randomly.tw. (1783)
- 70 (allocated adj2 random).tw. (703)
- 71 Single blind\$.tw. (11911)
- 72 Double blind\$.tw. (125667)
- 73 ((treble or triple) adj blind\$).tw. (263)
- 74 placebo\$.tw. (171422)
- 75 prospective study/ (199004)
- 76 or/58-75 (1231050)
- 77 case study/ (14928)
- 78 case report.tw. (221515)
- 79 abstract report/ or letter/ (824756)
- 80 or/77-79 (1056765)
- 81 76 not 80 (1196494)
- 82 51 and 57 and 81 (2878)
- 83 (2011\$ or 2012\$).em. (1317175)
- 84 82 and 83 (336)

This search was updated on 15 May 2013, and again on 5 February 2014.

## **Appendix 4. Cochrane Central Register of Controlled Trials**

- 1 exp Life Style/ (1848)
- 2 exp exercise/ or exp exercise therapy/ or exp relaxation techniques/ or exp walking/ or exp yoga/ (13798)
- 3 Life Style\$.tw. (230)
- 4 exercis\$.tw. (25842)
- 5 (walk\$ or jog or run or yoga).tw. (11305)
- 6 exp Diet/ (9692)
- 7 diet\$.tw. (20782)
- 8 (treatment\$ or therap\$).tw. (287111)
- 9 exp psychology/ or exp cognitive science/ or exp psychology, medical/ (731)
- 10 psycholog\$.tw. (8177)
- 11 (cognitive adj5 therap\$).tw. (3502)
- 12 psychotherap\$.tw. (2268)
- 13 meditation.tw. (367)
- 14 (biofeedback or hypnosis or reassur\$).tw. (2025)
- 15 ultraso\$.tw. (9144)
- 16 exp analgesics/ or exp clonidine/ or exp analgesics, non-narcotic/ or exp anti-inflammatory agents, non-steroidal/ or exp diclofenac/ or exp ibuprofen/ or exp naproxen/ or exp cyclooxygenase inhibitors/ (31219)
- 17 non-steroidal anti-inflammator\$.tw. (1089)
- 18 NSAIDS.tw. (1154)
- 19 exp Contraceptives, Oral/ (2830)
- 20 (oral contracept\$ or OCP).tw. (1584)
- 21 exp Progestins/ (1708)
- 22 (progestin\$ or progestogen\$).tw. (1379)
- 23 (danazol or GnRH analogue\$).tw. (451)



24 exp Antidepressive Agents/ (8730)

25 Antidepress\$.tw. (5618)

26 anticonvuls\$.tw. (527)

27 analges\$.tw. (19712)

28 caffeine.tw. (1704)

29 local anaesth\$.tw. (1915)

30 corticosteroid\$.tw. (6894)

31 (counselling or counseling).tw. (4514)

32 iucd.tw. (21)

33 transcutaneous nerve stimulation.tw. (73)

34 exp complementary therapies/ or exp acupressure/ or exp acupuncture therapy/ or exp electroacupuncture/ or exp moxibustion/ or exp holistic health/ or exp medicine, traditional/ or exp mind-body therapies/ or exp "biofeedback (psychology)"/ or exp hypnosis/ or exp "imagery (psychotherapy)"/ or exp meditation/ or exp relaxation therapy/ or exp yoga/ or exp phytotherapy/ or exp reflexotherapy/ (10237) 35 exp anesthetics, local/ or exp lidocaine/ (8493)

36 local anesthetic\$.tw. (2318)

37 referral\$.tw. (2888)

38 magnetic field\$.tw. (275)

39 sertraline.tw. (1089)

40 medroxyprogesterone\$.tw. (1246)

41 emotional disclosure.tw. (62)

42 reinforcement.tw. (1178)

43 goserelin.tw. (333)

44 dihydroergotamine.tw. (294)

45 lofexidine.tw. (62)

46 (chinese medicine\$ or chinese herb\$).tw. (1599)

47 pain relief.tw. (5639)

48 gonadotropin-releasing hormone analogue\$.tw. (64)

49 or/1-48 (370766)

50 exp Pelvic Pain/ (507)

51 (Pelv\$ adj1 Pain\$).tw. (390)

52 (Pelv\$ adj1 congest\$).tw. (11)

53 abdomin\$ pain\$.tw. (1687)

54 or/50-53 (2412)

55 49 and 54 (2000)

56 limit 55 to yr="2009 -Current" (275)

This search was updated on 15 May 2013, and again on 5 February 2014.

#### Appendix 5. AMED (Allied and Complementary Medicine)

1 (Pelv\$ adj1 Pain\$).tw. (105)

2 (Pelv\$ adj1 congest\$).tw. (4)

31 or 2 (109)

4 random.tw. (1984)

5 control.tw. (18120)

6 double-blind.tw. (1482)

7 clinical trials/ (1669)

8 placebo/ (517)

9 or/4-8 (22380)

10 3 and 9 (14)

This search was updated on 15 May 2013, and again on 5 February 2014.

### Appendix 6. Search strategy

YC816 Search string 09.09.09

Keywords CONTAINS "pelvic congestion" or "pelvic venous congestion" or "pelvic pain" or "chronic pain" or "chronic pelvic pain" or "pelvic" or Title CONTAINS "pelvic congestion" or "pelvic venous congestion" or "pelvic pain" or "chronic pain" or "chronic pain" or "pain-pelvic"

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomized trials which appears in the Cochrane Handbook of Systematic Reviews of Interventions (Version 5.0.2 chapter 6, 6.4.11)



The EMBASE search is combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/methodology/filters.html#random

There is no language restriction in these searches.

#### HISTORY

Protocol first published: Issue 11, 2010 Review first published: Issue 3, 2014

Date	Event	Description
30 October 2009	New search has been performed	This review was previously part of the review 'Interventions for treating chronic pelvic pain in women'. Due to the increase in the total number of studies, this review will now focus only on the non-surgical management of chronic pelvic pain. Another review on surgical management is also planned.

#### **CONTRIBUTIONS OF AUTHORS**

YCC performed the analysis and was the lead author in the writing of the review. GS contributed to the methodology and content of the review. AW contributed to the content and acted as a moderator.

#### **DECLARATIONS OF INTEREST**

None known.

#### **SOURCES OF SUPPORT**

## **Internal sources**

- · University of Southampton, UK.
- · University of Auckland, New Zealand.

#### **External sources**

· No sources of support supplied

#### DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review revises and updates the previous review entitled 'Interventions for women with chronic pelvic pain', which included only studies involving non-surgical interventions. Surgical interventions will be covered in a separate review.

## In the published protocol, we planned to consider the following six intervention groups.

- Medical interventions.
- Alternative/complementary therapies (such as magnetic field therapy, therapies encompassed in traditional Chinese medicine (acupuncture, herbal therapy, moxibustion), transcutaneous nerve stimulation and transcranial current stimulation).
- Psychological therapies (such as ultrasonography as a reassurance tool, written or oral emotional disclosures, counselling, cognitive therapy and biofeedback).
- Physical therapy (such as massaging and stretching).
- · Lifestyle (such as exercise and diet).
- Multidisciplinary/integrated approach: interventions combining two or more of the approaches described in the categories above.

### In the review, we considered the following three intervention groups.

- Medical interventions.
- Psychological treatments versus placebo/no treatment, or other interventions.
- Complementary treatments versus no treatment/sham or placebo or other interventions.



### **Rationale for change**

Interventions were regrouped using broader principles than those used in the protocol. Complementary and physical therapies were grouped together, as they aim to make a physical change to reduce pain, thereby achieving improved quality of life; psychological, educational and rehabilitative treatments were grouped together, as they aim to enable the person with CPP to manage the pain better, thereby achieving a better quality of life.

This regrouping is consistent with handling of physical, psychological and rehabilitative therapies in the Pain, Palliative and Supportive Care CRG (PaPaS) and with the rationales of the interventions. It allows some combination of studies, which otherwise would all be single studies, from which we could learn little. It is rare if not impossible for these interventions, which rely much more on the skills, training and orientation of the therapist than on a highly quality-controlled substance, to resemble one another much in practice.

#### **INDEX TERMS**

## **Medical Subject Headings (MeSH)**

Amines [therapeutic use]; Amitriptyline [therapeutic use]; Analgesics [adverse effects] [therapeutic use]; Chronic Pain [\*therapy]; Clonidine [adverse effects] [analogs & derivatives] [therapeutic use]; Contraceptive Agents, Female [adverse effects] [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Gabapentin; Goserelin [therapeutic use]; Medroxyprogesterone Acetate [adverse effects] [therapeutic use]; Pain Measurement; Pelvic Pain [\*therapy]; Psychotherapy; Randomized Controlled Trials as Topic; gamma-Aminobutyric Acid [therapeutic use]

#### MeSH check words

Female; Humans